Type 1 Diabetes Treatment Patterns and Glycemic Control in a Pediatric Cohort

by
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ABSTRACT

Type 1 Diabetes Mellitus (T1DM) is a chronic disease caused by an auto-immune response where the insulin producing cells in the pancreas are destroyed. Patents with T1DM do not produce any insulin; consequently, they must inject insulin and monitor blood glucose levels manually to attempt to maintain glycemic homeostasis. There is no cure for T1DM. Patients must focus on maintaining blood glucose levels to prevent morbidity from the disease. However, even tight control of blood glucose levels does not eliminate the risk of morbidity, and acute complications are common, especially in early childhood and adolescence. The high doses of injected insulin required to maintain glycemic homeostasis in T1DM patients put them at high risk of severe hypoglycemia (SH). Inadequate insulin, frequently caused by illness, is the primary cause of diabetic ketoacidosis (DKA).

The purpose of this dissertation was to describe demographics, initial care, and treatment patterns among T1DM patients and to estimate the effects of different treatment modalities on glycemic control and utilization of emergency care. We used insurance claims and electronic medical records (EMR) from the Department of Defense (DOD) Military Health Systems (MHS) database to create a cohort of pediatric T1DM patients, though different subsets of patients were used for each Aim depending on the requirements of each analysis. For the purposes of these analyses, a switch was defined as a change in insulin delivery method from multiple daily injections (MDI) to continuous subcutaneous insulin infusion (CSII) and an augment was defined as addition of a continuous glucose monitor (CGM) to self-monitoring of blood glucose (SMBG).

The first Aim focused on describing an incident cohort of T1DM patients. We found over 96% of patients in our cohort were using conventional therapy, consisting of MDI and SMBG, three months after diagnosis. During follow-up, more than half of patients switched insulin delivery to CSII, and about a third augmented with CGM. Nearly every patient who used a CGM had previously initiated CSII. Female gender, higher military rank of sponsor, and residing in the Central US were associated with a treatment change. We tested for trends in CSII and CGM use over time and found calendar year of T1DM diagnosis was not associated ($p=0.78$) with CSII use; however, CGM use significantly increased ($p<0.0001$) during the study period.

In Aim 2, we estimated the effect of a treatment change on the next hemoglobin A1c measurement. We found there was no interaction between switch and augment ($p=0.93$); however, changes in hemoglobin A1c after a switch or augment were depended on the A1c level before the treatment change. Improvements in hemoglobin A1c after a treatment change were, on average, higher among patients with poorer glycemic control. We estimated that patients with an initial hemoglobin A1c of 6% experienced no effect from a switch or augment. However, a patient with an initial A1c of 9% would experience a reduction of 0.55% ($p<0.0001$) from a switch and 0.30% ($p=0.002$) from an augment, and a patient with a hemoglobin A1c of 12% would experience a reduction of 1.13% ($p<0.0001$) from a switch and 0.51% ($p=0.007$) from an augment.

The purpose of the Aim 3 was to estimate differences in total emergency care utilization among patients initiating CSII and/or CGM compared to patients using MDI and/or SMBG. We observed 2.15 total emergency care days per patient year of follow-up. We estimated that CSII (RR = 0.81; $p<0.0001$) and CGM (RR = 0.88; $p<0.0059$)

decreased total emergency care days among patients initially using conventional therapy. Patients using both CSII and CGM experienced no additional benefit compared to those using CSII (with SMBG) or CGM (with MDI). CSII and CGM therapy were associated with a reduction in ER/ambulance days as well as hospitalization days. A secondary analysis of the effects of CSII and CGM on diabetes-related emergency care showed treatment choices may play an important role in both diabetes-related and total emergency care utilization.

Overall we found a substantial proportion of patients utilizing CSII and CGM. Changes in treatment were associated with reductions in hemoglobin A1c and decreased utilization of emergency care. Pediatric T1MD patients using conventional therapy who struggle to attain hemoglobin A1c levels less than 7.5%, the level of glycemic control recommended by the American Diabetes Association, may benefit from CSII and/or CGM.

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ABBREVIATIONS

ADA	American Diabetes Association
BMI	Body Mass Index
CGM	Continuous Glucose Monitor
CIT	Conventional Insulin Therapy
CPH	Cox Proportional Hazards
CSII	Continuous Subcutaneous Insulin Infusion (insulin pump)
DCCT	Diabetes Control and Complications Trial
DKA	Diabetic Ketoacidosis
DM	Diabetes Mellitus
DOD	Department of Defense
EMR	Electronic Medical Record
FDA	Federal Drug Administration
FIIT	Flexible Intensive Insulin Therapy
HR	Hazard Ratio
HRTx	Health Research Tx
ICD-9	International Classification of Diseases, Ninth Revision
IIT	Intensive Insulin Therapy
MDI	Multiple Daily Injections
MHS	Military Health Systems
RR	Rate Ratio
SH	Severe Hypoglycemia
SMBG	Self-Monitoring of Blood Glucose
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus

CHAPTER 1: INTRODUCTION

The purpose of this dissertation is to describe incident type 1 diabetic patients in terms of demographics, initial care, and treatment patterns and to asses if treatment choices affect glycemic control (hemoglobin A1c) and utilization of emergency care. This will provide valuable data that is currently unavailable. Our hope is the results of the study will help inform clinicians, patients, researchers, and policy makers about patterns of T1DM treatments and their effects on glycemic control.

Background

Type 1 Diabetes:

Diabetes mellitus is a chronic syndrome of impaired carbohydrate, protein, and fat metabolism due to insufficient production of the hormone insulin. The disease manifests in two main types. Type 1 Diabetes Mellitus (T1DM) is a chronic disease caused by an auto-immune response where the insulin producing cells in the pancreas are destroyed. Type 2 diabetes mellitus (T2DM) is typically caused by insulin resistance or reduced or delayed insulin production. T2DM patients may be able to control the disease by diet alone but medication is often necessary. Unlike T2DM, people with T1DM do not produce any insulin. As a result, T1DM patients must inject insulin several times daily to control their blood glucose levels. There is no cure for T1DM; therefore, patients must focus on maintaining blood glucose levels in order to prevent morbidity from the disease.[1] However, even tight control of blood glucose levels does not eliminate the risk of complications.

To maintain control over blood glucose levels, Type 1 diabetics must inject insulin, take multiple blood sugar readings daily, closely monitor their diet, and maintain

a healthy lifestyle. They must balance caloric intake with current blood sugar levels and expected daily exercise when determining how much insulin to take. Even small miscalculations in insulin dosages can result in high or low blood sugars. Consequently, most T1DM patients struggle or fail to maintain glycemic control.

Hemoglobin A1c measures a person's average blood sugar over the preceding three months and is the standard measure of long term glycemic control. Normal hemoglobin A1c levels for non-diabetic persons range from 4 to 6%, indicating average blood sugars of 70 to 126 mg/dL, respectively. The American Diabetes Association (ADA) recommends pediatric patients maintain a hemoglobin A1c of 7.5% or less.[2] A 2011 study of nearly 21,000 T1DM patients found the average hemoglobin A1c to be 8.18%, suggesting the average T1DM patient has an average blood sugar of 214 mg/dL.[3] Maahs et al. recently found that only 22% of US children are meeting the current ADA goal.[4] Studies have shown that fear of hypoglycemia is a major contributor to difficulties reaching hemoglobin A1c goals.[5,6,7]

Though most low blood sugar events are mild and easily corrected by eating or drinking carbohydrates with a high glycemic index, severely low blood sugar levels can be acutely dangerous leading to unconsciousness, coma, and even death. Multiple episodes of severe hypoglycemia (SH) can result in seizures, cardiovascular disease, and cognitive decline.[8] Long term consequences of chronically high blood glucose levels include: retinopathy[9], neuropathy[10], digestive disorders[11], cardiovascular disease[12], and kidney disease.[13]

Epidemiology:

There are approximately 1 million people in the Unites States living with type 1diabetes, and the economic burden is estimated at nearly $15 billion annually.[14] The CDC estimates between 2002 and 2005, there were 15,600 incident cases of T1DM annually in people under the age of 20 in the US.[15] Globally, the incidence of T1DM is increasing by 2 to 4% annually. Though incidence of T1DM was steady in the US from 1980's through the 1990's, recent research estimates incidence has been increasing by 2.3% annually since 2000.[16] Simulations have projected the prevalence of type 1 diabetes among US children may double or triple by the year 2050.[17] The causes behind the increasing trend in global incidence are unknown.[18]

The majority of type 1 diabetic patients will suffer morbidities from the disease. A US study found after 30 years of T1DM, 50% of patients reported retinopathy, 25% reported kidney disease, and 14% reported cardiovascular disease.[19] A Polish study found among individuals with at least a 20 year history of T1DM, only 1 in 10 patients was free of any microvascular complication.[20] Studies have generally estimated the standardized mortality ratios (SMRs) of T1DM patients to be between 2 and 5, and a Norwegian study estimated an SMR of 20 for ischemic heart disease.[21]

Modes of Treatment:

Treatment for type 1 diabetes involves injecting insulin subcutaneously and monitoring blood glucose levels. Methods for injecting insulin include multiple daily injections (MDI) and continuous subcutaneous insulin infusion (CSII), also known as an insulin pump. Patients who treat with MDI typically inject a long acting (basal) insulin as

a base as well as rapid-acting (bolus) insulin for meals and high blood glucose correction. Patients using CSII use only rapid-acting insulin. The pump is programmed to continuously deliver insulin at a programmed basal rate and will deliver bolus insulin for meals or blood glucose correction when manually instructed to do so. Methods for monitoring blood glucose levels include self- monitoring of blood glucose (SMBG) and use of a continuous glucose monitor (CGM). SMBG is achieved by pricking one's finger multiple times daily to measure a blood glucose level. A CGM is a device that is attached to the patient and continuously reads glucose levels in interstitial fluid using a wire sensor inserted in the skin. While all T1DM patients are advised to make insulin dosing decisions based on finger stick blood sugars, CGM can be used to estimate blood glucose as well as indicate whether glucose levels are increasing, decreasing, or remaining steady.

Effectiveness of Treatment Modalities:

Studies measuring the effects of CSII and/or CGM usage compared to conventional therapy (injections and finger stick blood sugars) on glycemic control have demonstrated mixed results. A recent systematic review comparing MDI with CSII concluded there was no difference in hemoglobin A1c levels among children, though adults' A1c levels were on average 0.3% lower with CSII.[22] However, studies suggest there may be decreased risk of ketoacidosis and severe hypoglycemia among patients using CSII. [23,24,25] Clinical trials of CGM in children have generally not demonstrated clinically meaningful differences in glycemic control except in those with strict adherence or high hemoglobin A1c levels at baseline.[26,27] Evidence of the effectiveness of CGM use at reducing risk of acute complications of T1DM is mixed, with some studies

suggesting a reduction in SH and/or DKA[28,29,30] and some finding no association.[31,32] Trials of sensor augmented insulin pumps (a system containing CSII integrated with a CGM) have consistently shown improvement in hemoglobin A1c, mean blood sugar, and reduced time spent in hyperglycemia and hypoglycemia for children and adults.[33,34,35]

Identifying patients in EMR/Claims databases:

Pharmacoepidemiological studies utilize electronic medical record (EMR) and insurance claims databases as time and cost-efficient sources of patients and medical information for public health research. These studies typically rely on International Classification of Diseases, Ninth Revision (ICD-9) codes to detect and differentiate diseases. ICD-9 codes have been shown to have a high positive predictive value when identifying T1DM patients.[36] Several studies have developed algorithms including patient demographics, laboratory measures, medical encounters, and prescription data to identify pediatric diabetic patients and differentiate between T1DM and T2DM patients.[37,38,39,40] These studies have been able to achieve algorithms with high sensitivity, specificity, and positive predictive value.

Significance

The treatment patterns of pediatric type 1 diabetic patients are not well described in the literature. Aim 1 of this dissertation was designed to identify and describe a pediatric cohort with incident type 1 diabetes. Patients were identified using a data driven algorithm designed to identify T1DM patients with high specificity. We were able to follow these patients through time and observe changes in treatment as they occurred.

The purpose of Aim 2 and Aim 3 was to estimate the effects of changing treatment (switching to CSII and/or augmenting with CGM) on measures of glycemic control. Most studies describing these therapies are clinical trials and are generally designed to answer the question: *Do patients initiating CSII and/or CGM experience improved glycemic control compared to patients who continue to use conventional therapy?* These trials are designed to measure the treatment effects associated with a CSII and/or CGM. However, patient experiences may differ from the estimated true effects. Changes in glycemic control measured in observational studies equal the sum of the true treatment effects and other influences, such as patient motivation and adherence. We, therefore, attempted to answer a slightly different question: *Do patients who initiate CSII and/or CGM in a typical care setting experience subsequent improvements in glycemic control?* This is an important question as effects of treatment experience outside a trial setting could theoretically be larger or smaller than predicted. Our goal was to estimate changes in measures of glycemic control after initiation of CSII and/or CGM in a typical care setting.

Specific Aims

Specific Aim 1: Describe characteristics at presentation, treatment patterns, predictors of treatment modality, trends in treatment over time, and switching and augmentation patterns in a pediatric population with incident T1DM using data from the Department of Defense Military Health Systems electronic medical record and insurance claims database.

Specific Aim 2: Estimate changes in hemoglobin A1c after initiation of CSII and/or CGM compared to changes in hemoglobin A1c among patients who continue using MDI and/or SMBG in a pediatric population with T1DM for at least a year using data from the Department of Defense Military Health Systems electronic medical record and insurance claims database.

Specific Aim 3: Estimate changes in emergency care utilization after initiation of CSII and/or CGM compared to changes in emergency care utilization among patients who continue using MDI and/or SMBG in a pediatric population with T1DM for at least a year using data from the Department of Defense Military Health Systems electronic medical record and insurance claims database.

Conceptual Framework

The Aims in this dissertation are organized so each subsequent Aim builds on the results of the work preceding it. In Aim 1, T1DM patients will be identified and described in terms of treatment patterns and associated characteristics. Aim 2 will use the information gathered in Aim 1 to build a model that will attempt to estimate differences in hemoglobin A1c subsequent to a change in treatment. Aim 3 will take this a step further by trying to estimate if treatment changes effect emergency care utilization. The conceptual framework is displayed in Figure 1 and the main analyses of each Aim are displayed in Figure 2.

Figure 1: Conceptual Framework.

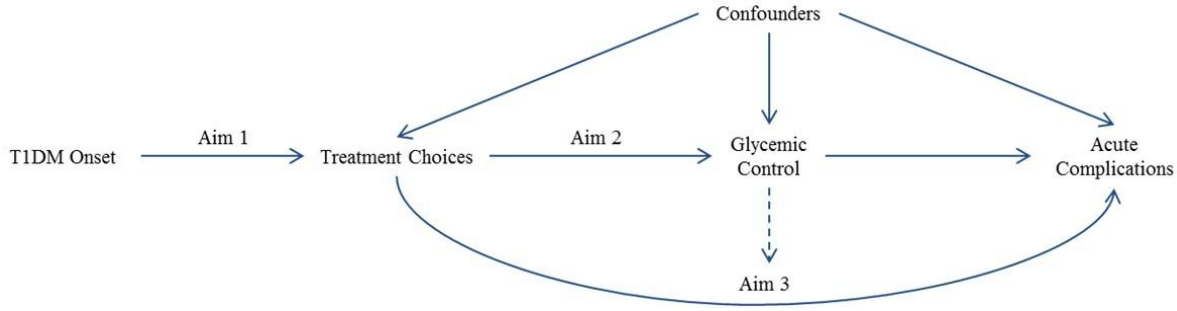
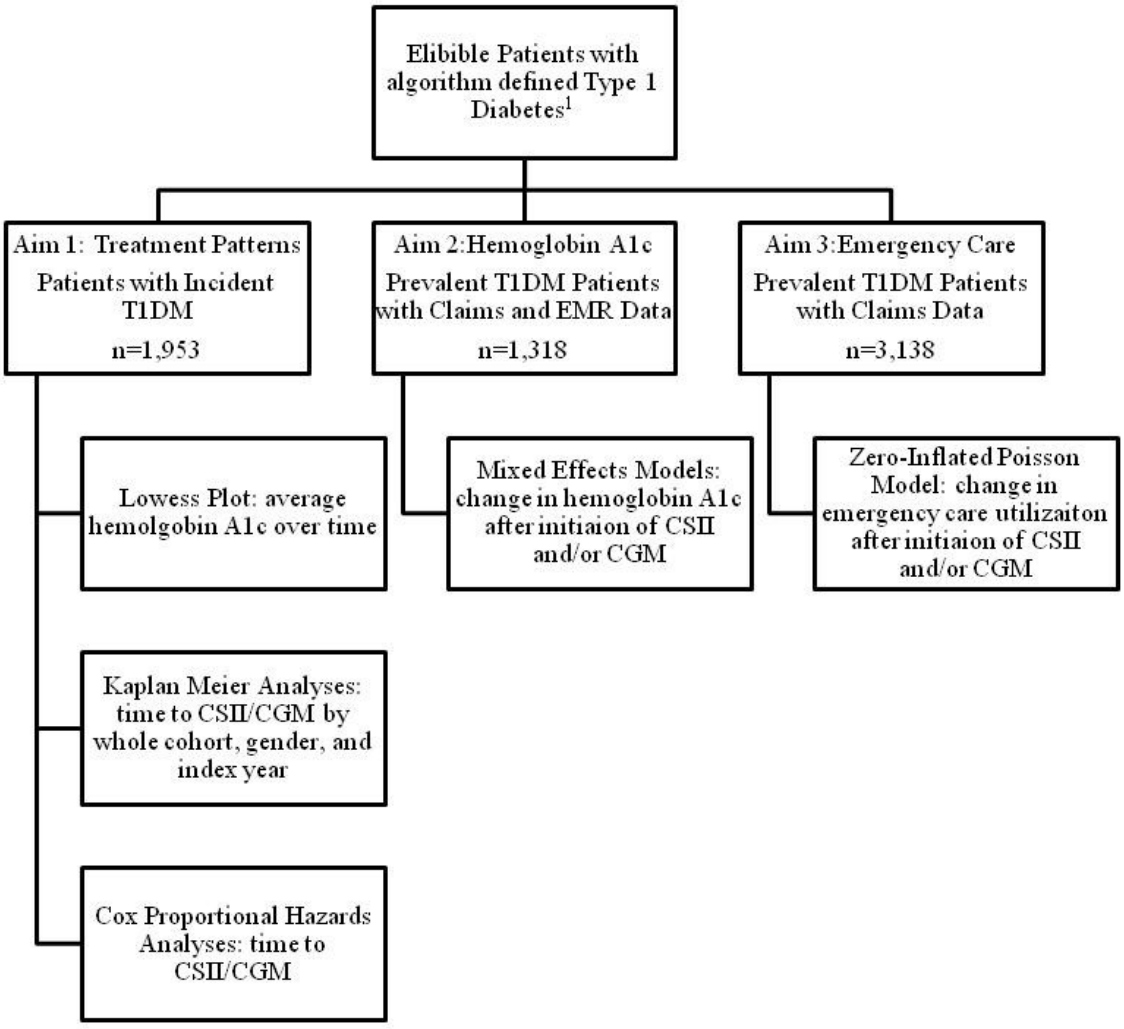


Figure 2: Diagram of Main Analyses.



[1]All patients included in this study had type 1 diabetes based on an algorithm we defined during exploratory analysis: at least two T1DM medication orders on separate days and (at least one T1DM diagnostic code or zero T2DM diagnostic codes).

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CHAPTER 2: MANUSCRIPT 1 – TREATMENT PATTERNS

Abstract

Purpose: The purpose of this study was to identify an incident cohort of pediatric patients with type 1 diabetes mellitus (T1DM) and to describe their medical and demographic characteristics, treatment patterns, and predictors of treatment at diabetes presentation and during follow-up.

Methods: This study was performed using data extracted from the US Department of Defense (DOD) Military Health Systems (MHS) database between October 2007 and September 2013. Exploratory analyses were performed to develop an algorithm designed to identify diabetic patients and differentiate between type 1 and type 2 diabetes. Patients were described in terms of medical and demographic characteristics and treatment patterns. We performed Kaplan Meier and Cox proportional hazards analyses to estimate characteristics predictive of continuous subcutaneous insulin infusion (CSII) and continuous glucose monitor (CGM) use.

Results: We identified 1,953 pediatric patients with incident type 1 diabetes as defined by our algorithm. The majority (96.3%) of patients in our cohort used conventional therapy at type 1 diabetes presentation. Survival analysis showed more than half (57.1%) of patients initiated CSII and about a third (32.62%) initiated CGM during follow-up. Most (81%) patients who initiated CGM did so at the same time or after initiating CSII. We found younger age ($p<0.0001$), female gender ($p<0.0001$), and higher military rank of sponsor ($p<0.0001$) were independently associated with a treatment switch or augment. In multivariate analyses, previous use of CGM was the best predictor

of CSII initiation (HR=2.5; [95% C.I., 1.74 – 3.30]), and previous use of CSII was the best predictor of CGM use (HR=22.79; [95% C.I., 18.13 – 28.64]). We tested for trends in CSII and CGM use over time and found calendar year of T1DM diagnosis was not associated ($p=0.78$) with CSII use; however, CGM use significantly increased ($p<0.0001$) during the study period.

Conclusion: We were able to identify an incident cohort of type 1 diabetic patients and describe their treatment patterns and associated characteristics. Initiation of CSII and CGM was common in this young cohort of patients with T1DM. More research would be needed to determine if the treatment patterns we observed are typical of other T1DM populations.

Introduction

Type 1 diabetes mellitus (T1DM) is one of the most important pediatric chronic diseases in the United States, affecting more children than cancer.[1] Today, approximately 1 million people in the United States are living with T1DM,[2] with roughly one in 500 children affected.[3] Research indicates that T1DM incidence is rapidly increasing[4,5,6] and that the prevalence among US children may double or triple by the year 2050.[7]

Type 1 diabetes is an auto-immune disease where the insulin producing (beta) cells in the pancreas are completely destroyed. Consequently, T1DM patients create no insulin of their own and must inject insulin to live. There are two options for injecting insulin: multiple daily injections (MDI) and continuous subcutaneous insulin infusion (CSII), also referred to as insulin pumps. T1DM patients must also constantly monitor blood glucose levels. The two options for monitoring blood glucose include self-monitoring of blood glucose (SMBG) and use of a continuous glucose monitor (CGM). SMBG is achieved by pricking one's finger multiple times daily to measure a blood glucose level. A CGM is a device that is attached to the patient and continuously reads glucose levels in interstitial fluid using a wire sensor inserted in the skin.

Continuous subcutaneous insulin infusion more closely imitates the body's natural metabolic processes compared to multiple daily injections. The benefits of using CSII include improved quality of life and reduced glycemic variability, and possibly, reduced risk of severe hypoglycemia and diabetic ketoacidosis.[8,9] Patients who use CSII demonstrate much higher treatment satisfaction compared to those using MDI.[10,11] CSII has also been shown to reduce daily insulin requirements by 21%.[12] Yet barriers to CSII persist, including negative patient perceptions[13] and the high cost of treatment,[14,15] and

evidence that CSII (compared to MDI combining fast and long-acting insulins) reduces hemoglobin A1c is mixed.[16,17,18]

Continuous glucose monitoring offers several benefits over self-monitoring of blood glucose. While a single finger prick blood sugar gives the glucose reading for a single point in time, a CGM provides a reading every few minutes so patients may more easily recognize patterns and trends throughout the day. Furthermore, because glucose readings are continuous, a CGM may warn patients of high or low blood sugars via preset alarms before they would have otherwise known. Patients using CGM have reported less fear of hypoglycemia and improved empowerment and quality of life.[19] However, clinical trials have not shown meaningful improvements in hemoglobin A1c in pediatric populations,[20,21,22] or reductions in severe hypoglycemic events,[23] though they have demonstrated reduced time in hypoglycemia (blood glucose < 70 mg/dL).[24]

Despite the potential benefits of CSII and CGM, many patients continue to use conventional therapy (MDI and SMBG). Motivations for treatment choices among T1DM patients are not well studied; though, it is likely that reluctance to use CSII and CGM is largely due to high associated costs of treatment, invasiveness, and perceived body image and social acceptance.[25,26,27,28] Manufacturer data from 2006 suggested nearly a quarter of type 1 diabetic patients in the United States were using CSII.[29] However, to our knowledge, there have been no studies describing treatment patterns in pediatric T1DM populations in the United States. The primary objective of this study was to identify a cohort of incident pediatric T1DM patients and describe their treatment patterns at first diagnosis and during follow-up. We also aimed to describe our cohort in

terms of medical and demographic characteristics at disease presentation and estimated which characteristics were predictive of treatment modality.

Methods

Study Population

This study was performed using data extracted from the US Department of Defense (DOD) Military Health Systems (MHS) database. The DOD MHS serves active and past military personnel (known as the sponsor) and their dependents. The database includes both an electronic medical record (EMR) and a medical insurance claims component. All patients are included in the insurance claims data, and approximately one third have EMR data. Data collected includes: demographics, diagnostic codes, information on medical procedures, symptoms, vital signs, laboratory and radiology results, and pharmacy orders and claims. The crude data, prepared by Health Research Tx (HRTx), included all EMR encounters and insurance claims for patients with at least one International Classification of Diseases, Ninth Revision (ICD-9) diagnostic code indicating diabetes (250.XX) before their 19th birthday. All personally identifiable information was removed. At the time of extraction, data were available between October 2007 and September 2013. Our first objective was to use these data to create a cohort of patients with incident T1DM.

Patients in the DOD MHS dataset during the study period meeting the following criteria were selected for this study:

- At least one of the following:
    - One hospitalization with an ICD-9 diagnostic code for DM (250.XX)

    - Two DM diagnostic codes within one year
    - One diagnostic code for DM and one treatment for DM
- Age 18 years or younger at first diabetes diagnosis
- A minimum of 6 months of enrollment (baseline period) before first DM diagnosis
- A minimum of 4 months of enrollment after first DM diagnosis

Among patients meeting the eligibility criteria, the first day where an eligible patient had a diabetes-related ICD-9 (250.XX) or medication was considered the index day for the study. The requirement for a 6-month baseline enrollment period before the index day was designed to help create a cohort with new onset diabetes. We required at least 4 months of follow-up to allow time for measurement of treatment patterns after diabetes presentation.

Exclusion criteria were chosen to reduce the number of patients with gestational or other secondary (non-type 1 or 2) diabetes. Patients meeting the following criteria were excluded from the study:

- Patients becoming pregnant less than four months after index date were excluded. (Patients becoming pregnant greater than four months after index were censored at the pregnancy date.)
- Patients with an ICD-9 code indicating any of the following: secondary diabetes (249.x), other endocrine dysfunction (251.8), adrenal cortical steroids causing adverse effects in therapeutic use (E932.0), adenocarcinomas (151.0), lupus erythematosus (710.0, 695.4), cystic fibrosis (277.0, 277.0X), hemochromatosis (275.0), acromegaly (253.0), Cushing's syndrome (255.0), Down syndrome

(758.0), Klinefelter syndrome (758.7), Turner syndrome (758.6), Huntington chorea (333.4), or Laurence-Moon-Biedl syndrome (759.89).

Diabetes Type Algorithm

Previous studies have shown T1DM diagnostic codes and insulin prescriptions can be used to identify pediatric T1DM patients in claims and EMR data with high specificity.[30,31,32,33] Using this information, we performed exploratory data analyses to develop an algorithm to differentiate between type 1 and type 2 diabetes in the MHS data. To achieve this, we created a cohort of patients with only type 1 (250.x1or 250.x3) or with only type 2 (250.x2) ICD-9 diagnostic codes. The characteristics of these patients were used to differentiate between diabetes types for those patients where diagnostic codes were of mixed type or only included unspecified diabetes (250.00).

Mode of Diabetic Treatment

Patients identified as T1DM were described in terms of initial treatment. As it can take several weeks for insurance companies to approve CSII or CGM usage, initial treatment was defined as the treatment a patient was using 90 days after the index day. Patients were divided into the following four groups:

- MDI and SMBG (conventional therapy)
- MDI and CGM
- CSII and SMBG
- CSII and CGM

For the purposes of this study, a treatment "switch" was defined as a change in insulin delivery method, from multiple daily injections to continuous subcutaneous insulin infusion. An "augment" was defined as initiation of CGM, as CGM use is meant to be in addition to self-monitoring of blood glucose. We described switching and augmentation patterns among those patients using conventional therapy at index.

Statistical Analyses

After diagnosis, patients with type 1 diabetes frequently experience a temporary period of partial remission called the "honeymoon period" where the pancreas continues to secrete a small amount of insulin.[34] Because we hoped to identify an incident cohort, we hypothesized that hemoglobin A1c values for the study population should fall sharply after index and then rise again as the honeymoon period, and thus endogenous insulin secretion, ends. We created a Lowess plot of hemoglobin A1c over time to determine if we could observe this phenomenon.

We created means and frequency distributions of patient characteristics to describe the study population as a whole and by index treatment group. We calculated statistical significance of continuous variables using a t-test and significance of binary and categorical variables using a chi square statistic.

We estimated differences in time to switch/augment by gender and year of diagnosis by Kaplan Meier analysis using a Log-Rank test for the statistical significance of differences between groups. Finally, we created a multivariate Cox Proportional Hazards (CPH) model using backwards selection from variables significantly associated

with switch/augment in bivariate analyses. Separate models were created for time to initiation of CSII and time to initiation of CGM using claims and EMR data.

All statistical analyses were performed on the HRTx Citrix server using SAS version 9.3.

Results

Diabetes Type Algorithm

A total of 3,757 patients were eligible for this study (see Figure 1); however, diabetes type for these patients was unknown. We found 94% of patients with only type 1 ICD-9 codes had multiple medication orders for insulin, while 82% of patients with only type 2 codes had none. The final differentiating algorithm [at least two T1DM medication orders on separate days and (at least one T1DM diagnostic code or zero T2DM diagnostic codes)] identified 1,953 algorithm-defined T1DM patients.

Patient Characteristics

Our study population consisted of 1,953 individuals including 1,071 males and 882 females. The average age at T1DM presentation was 12.4 years old. Among patients with EMR data, the average hemoglobin A1c at index was 11.6% and the average BMI was 20.1 kg/m^2. Hospitalizations were rare during the 6-month baseline period; however, 14.2% of patients visited the emergency room during this time. The index therapy for nearly all (n=1,881; 96.3%) patients was MDI and SMBG (conventional therapy); few patients used CSII and SMBG (n=62; 3.2%), MDI and CGM (n=3; 0.2%), or CSII and

CGM (n=7; 0.4%) within the first three months after index. Patient characteristics by index treatment group (MDI vs. CSII) are displayed in Table 1. At T1DM presentation, 59.2% of patients received care in the emergency room and 65.3% were hospitalized. Younger patients were more likely to be hospitalized ($p<0.0001$) compared to older patients (See Table 2). Patient selection and treatment patterns at index and follow-up are displayed in Figure 1.

Hemoglobin A1c

The average hemoglobin A1c during the duration of the study was 8.8%. The Lowess plot of hemoglobin A1c clearly showed the effects of uncontrolled hyperglycemia at index followed by the honeymoon period. The plot predicted a decrease in A1c from 12.2% at T1DM presentation to 7.2% three months later. Average A1c values then steadily increased until stabilizing at around 8.7% approximately 12 to 14 months after presentation. The average hemoglobin A1c after the first year of diabetes was 8.7%. The Lowess plot of hemoglobin over time is displayed in Figure 2.

Treatment Patterns at T1DM Presentation

Because so few (n=10) patients were using a CGM at index, we were unable to test the statistical significance of differences between them and patients using SMBG. However, we were able to evaluate differences between CSII users (n=69) and patients using MDI (n=1,884). CSII users were more likely to be female ($p=0.029$), had lower BMI ($p=0.048$), higher military rank of sponsor ($p=0.028$), were less likely to visit the ER during baseline ($p=0.0.004$), less likely to visit the ER at index ($p=0.001$), and less

likely to be hospitalized (p=0.001) than those using MDI. The difference in index hemoglobin A1c was not statistically significant (p=0.29between treatment groups.

Treatment Patterns During Follow-up

Nearly half (n=813; 43.2%) of patients on conventional therapy at index had a change in treatment (initiated CSII and/or CGM) during the study period. Among patients who changed treatment, 770 (94.7%) initiated CSII therapy and 319 (39.2%) initiated CGM. Very few patients who changed treatment initiated CGM alone (n=43; 5.3%) or before beginning CSII (n=19; 2.3%). Thus, the predominate pattern among patients using conventional therapy at index who initiated both CSII and CGM (n=276; 14.7%) was for patients to initiate CSII and CGM at the same time (n=137; 7.3%) or to add CGM after a CSII (n=120; 6.4%). The treatment patterns for patients using conventional therapy at index is displayed in Table 3.

Exploratory analyses showed T1DM patients who chose to switch to CSII were characteristically very similar to those who chose CSII and CGM, largely because they were the same patients. However, because so few patients (n=42) chose only to augment with CGM, we were unable to determine if the characteristics of these patients were significantly different than other switch/augmenters. Additionally, we performed a sensitivity analysis where augment only patients were removed. There were no differences in the number of statistically significantly associated variables between the full and the sensitivity analysis models. Therefore, we decided to group switch and augmenters together into a single group when analyzing statistical significance of predictors of treatment change.

In bivariate analyses, patients who changed treatment were more likely to be female ($p<0.0001$), were on average 1.4 years younger at index ($p<0.0001$), had a mean BMI 4.1 kg/m^2 lower ($p<0.0001$), higher military rank of sponsor ($p<0.0001$), were less likely to visit the ER during baseline ($p=0.008$), and were less likely to be hospitalized at index ($p=0.004$) compared to patients who continued using conventional therapy during follow-up. While geographic region and military branch were statistically significantly associated with a treatment change, the distribution of those variables was not strikingly different between treatment change groups. Patient characteristics by treatment change group are displayed in Table 4.

Five years after diabetes presentation, the cumulative proportion of patients who had initiated CSII (Figure 3) and CGM (Figure 4) was 57.1% and 32.6%, respectively. Analyses demonstrated females were more likely to switch ($p<0.001$) or augment ($p=0.006$) than males (displayed in Figures 5 and 6, respectively). However, once a patient had switched to CSII (Figure 7), there was no association between gender and augment ($p=0.92$). There was no association ($p=0.77$) between index year and switch to CSII (Figure 8); however, there was a strong association between index year and augment with CGM ($p<0.001$). Figure 9 clearly displays that with each successive index year, patients augmented with CGM more quickly.

In multivariate analyses (Tables 5 through 7), patients were more likely to switch mode of insulin delivery from MDI to CSII if they had previously used a CGM (HR=2.40; $p<0.0001$), were female (HR=1.28; $p=0.0004$), or younger in age (HR=0.94; $p<0.0001$). Geographic region ($p=0.0079$) and higher military rank of sponsor ($p<0.0001$) were also associated with switching. Initiation of CGM was strongly associated with

previous CSII use (HR=22.79; p<0.0001) and calendar year of diabetes index (p<0.0001). No other variables were predictive of CGM use in this model. Calendar year of diagnosis was not associated with initiation of CSII (p=0.78) but was strongly associated with CGM. Patients diagnosed with T1DM in 2013 were much more likely to use a CGM compared to those diagnosed in 2008 (HR=13.74; p<0.0001).

Because CSII was so strongly predictive of future CGM use, we performed an additional analysis of time to augment restricted to CSII users. In this analysis, geographic region (p=0.0483), military branch of sponsor (p=0.0048), and year of diabetes index (p<0.0001) were associated with CGM use. Patients who presented with T1DM in 2013 were more likely to initiate CGM (HR=4.87; p<0.0001) compared to those diagnosed at the beginning of the study.

Index BMI was associated with initiation of CSII (HR=0.89; p<0.0001) and CGM (HR=0.90; p=0.0001) in bivariate analyses; though, index hemoglobin A1c was associated with neither. Approximately one fourth (26.2%; n=512) of our cohort had a measurement for index BMI. Among these patients, 225 (43.2%) initiated CSII and 83 (15.9%) initiated CGM. Index BMI (HR=0.89; p= p<0.0001), geographic region (p=0.0114), and military rank of sponsor (p=0.0117) were associated with CSII use and previous CSII use (HR=27.00; p<0.0001), index BMI (HR=0.94; p=0.0253), and index year (p<0.0001) were associated with CGM. Results of the multivariate models using EMR data are displayed in Table 8 for initiation of CSII and Table 9 for initiation of CGM.

Discussion

Summary of Main Findings

While the vast majority of patients in our cohort started on conventional therapy (96.3%), over half (57.14%) switched insulin delivery from multiple daily injections to continuous subcutaneous insulin infusion and about a third (32.62%) augmented with a continuous glucose monitor. Nearly every patient who augmented with a CGM, had previously initiated CSII. As expected, hemoglobin A1c levels clearly demonstrated a "honeymoon period," falling sharply after diagnosis until month 3, then steadily rising until about one year after presentation. The best predictor of CSII initiation was previous initiation of CGM; likewise, the best predictor of CGM initiation was previous initiation of CSII. Female gender, geographic region, and military rank of sponsor were also predictive of CSII. BMI was inversely associated with initiation of CSII and CGM. Year of diagnosis was not associated with initiation of CSII ($p=0.78$); however, CGM use was increasing ($p<0.0001$) during the study period.

Emergency Care at Presentation

The low frequency of ER admission and hospitalization during the 6-month baseline and the high rates of ER admission and hospitalization at index are evidence that we correctly identified the first presentation of T1DM. In the United States, the prevalence of diabetic ketoacidosis (DKA) at T1DM presentation is estimated to be between 25% and 50%.[35] This is in line with our findings, as *post hoc* analyses showed 46.8% of the hospitalizations at index contained an ICD-9 diagnostic code for DKA (250.1X) indicating that approximately 31% of our cohort had DKA at presentation. The

high rate of DKA and emergency care at diabetes presentation demonstrates that the majority of T1DM patients are not identified until they become very ill.

Hemoglobin A1c and BMI

Approximately 70% of T1DM patients enter a "honeymoon" phase after diagnosis where insulin requirements are reduced and glycemic control is increased.[36] Studies have shown that the proportion of patients in honeymoon peaks at approximately 3 months after diabetes presentation and then gradually falls so few patients are still in honeymoon more than one year after diagnosis.[37,38] Because we intended to describe treatment patterns in an incident cohort, we hypothesized *a priori* that we should be able to observe this phenomenon. This pattern is demonstrated by our Lowess plot of mean hemoglobin A1c over follow-up (Figure 1). Furthermore, mean hemoglobin A1c values observed in this study are similar to other cohort studies.[39,40,41]

Symptoms of T1DM begin to appear once 80-90% of pancreatic beta cells are destroyed.[42] As endogenous insulin production decreases, glucose cannot be metabolized and is excreted in the urine. Consequently, one of the hallmark symptoms of new onset T1DM, along with polyuria and polydipsia, is weight loss,[43,44] and T1DM patients are frequently underweight at presentation.[45,46] The average BMI among patients in our cohort was much lower than would be expected in a healthy pediatric population. The hemoglobin A1c and BMI properties of our cohort are further evidence that we were able to identify incident T1DM patients in the DOD MHS database with some specificity.

Continuous Subcutaneous Insulin Infusion

Initiating CSII was associated with increasing military rank of sponsor (our socio-economic surrogate), younger age at diagnosis, and female gender. These findings are consistent with those of other observational studies.[47,48] It is likely that families with higher incomes are better able to afford the high cost of CSII therapy. Also, CSII is especially suited for young patients due to the precision needed to administer small amounts of insulin and increased parental involvement in disease management compared to older adolescents. While it is difficult to speculate why females would be more likely to use CSII than males, studies have shown that females have higher hemoglobin A1c levels and are more likely utilize emergency care compared to males.[49,50,51] It may be that increased use of CSII in females demonstrates efforts to increase glycemic control, though there are likely many other factors involved in treatment choices.

The first CSII pumps were developed in the late 1970's,[52,53] though it was in the late 1990's, after their safety and efficacy had been widely established, when use of CSII began rapidly increasing in pediatric populations. [54,55] However, in our cohort, we did not detect any change in the prevalence of CSII use over time. This suggests that during the period from 2008 to 2012 CSII use patterns were stable, at least in our study population.

Continuous Glucose Monitors

In our cohort, patients initiating CGM consisted primarily of a subset of patients using CSII. Consequently, the strongest predictor of initiation of CGM was previous CSII use. This observation suggests that motivations for initiation of CGM may be similar to

those for initiation of CSII, appealing to the same people. However, to our knowledge, there are no studies describing motivations for CGM use.

The first CGM intended for patient use was approved by the FDA in 2005 and became commercially available in 2006. However, no CGM was approved for pediatric use until 2014. When designing this study, we were aware of the possibility that we would not detect significant CGM use in our cohort as it had not been approved by the FDA for this population during the study period. However, we observed nearly one third of the patients in our study initiated CGM during the study period demonstrating that off-label use of CGM was fairly common. We also detected a strong secular trend of increasing prevalence for each calendar year during the study period. This trend makes sense as CGM therapy is a relatively new, and still improving, technology.

Strengths and Limitations

Our data suggests we were able to identify an incident cohort of type 1 diabetic patients. Identifying the date of T1DM presentation allowed us to measure index treatment as well as treatment changes in continuous time during follow-up. This is important in situations where more than one treatment combination is possible. For example, we observed that initiation of CGM rarely occurs before initiation of CSII. This trend would be more difficult to detect among a prevalent T1DM population because among patients using both, you would not know which treatment was initiated first.

This study was completed using EMR and insurance claims data, which has several strengths and limitations. Electronic data are readily available and are an efficient method for measuring outcomes for large cohorts of patients. Also, using claims data to

describe treatment patterns of T1DM patients should capture nearly all insulin, CSII, and CGM related purchases as these treatments are expensive and unlikely to be paid for out of pocket. EMR data (BMI and/or hemoglobin A1c) was only available for about one third of the patients in our cohort. However, at index, having a measurement for BMI ($p=0.50$) or hemoglobin A1c ($p=0.15$) was not associated with CSII, and having a measurement for BMI ($p=0.65$) or hemoglobin A1c ($p=0.14$) was not associated with a treatment change during follow-up.

There was likely some misclassification of diabetes type. Identification of patients with T1DM was based on algorithms developed during exploratory data analyses. It is possible, however, that some T1DM patients were missed and some T2DM patients were wrongfully included. Omission of T1DM patients may have reduced statistical power and could have resulted in selection bias. Our differentiating algorithm was designed to be specific (rather than sensitive), so we believe it is unlikely many patients with T2DM were wrongfully classified as type 1. This may reduce generalizability if patients who were omitted were characteristically different or would have demonstrated different treatment patterns during follow-up.

Another limitation of EMR/claims data is the lack of information on important confounders. For example, we were unable to adjust for sociodemographic indicators, including race and ethnicity, in our analyses because this information was missing for more than 99% of patients. However, studies have shown socioeconomic characteristics, such as higher education and income, are superior predictors of CSII and CGM use compared to sociodemographic factors.[56,57,58] While we did not have household income or education data, we were able to use military rank of sponsor in our analysis, which we

believed could be a socioeconomic indicator. We observed a strong relationship between increasing military rank of sponsor and increased likelihood of CSII/CGM use, which supports the hypothesis that rank of sponsor may be a socioeconomic indicator.

T1DM patients identified in this study may not be representative of the pediatric T1DM population in the United States. As the dependents of active and past military personnel, patients in this study are likely demographically different than the general US pediatric population and likely experience different levels of healthcare. Consequently, the treatment patterns observed in this study may not be typical of all incident T1DM patients.

Conclusion

The purpose of this study was to identify a cohort of patients with incident T1DM and to describe patient characteristics at presentation, predictors of treatment, and treatment patterns at index and during follow-up. We found 96% of patients were using conventional therapy (MDI and SMBG) shortly after diabetes presentation. During follow-up, more than half of patients initiated CSII and about a third initiated CGM. Most patients who initiated CGM had previously initiated CSII, suggesting that these treatment appeal to the same subset of T1DM patients. Calendar year of diagnosis was associated with initiation of CGM suggesting that CGM is becoming a more common treatment among pediatric T1DM patients. More research is needed to determine if the treatment patterns we observed in this study are typical of other T1DM populations. Further, research into the underlying motivations behind treatment choices would also be beneficial.

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Tables

Table 1: Patient Characteristics by Index Treatment CSII Group (n=1,953).

Patient Characteristic	MDI (N=1,884)	CSII (N=69)	P-value*
Gender [n (%)]			
Female	842 (44.7%)	40 (58.0%)	0.029
Male	1042 (55.3%)	29 (42.0%)	
Age on Index Day [mean (SD]	12.4 (3.3)	13.0 (3.9)	0.17
Patients with Index BMI Value [n (%)]	505 (26.8%)	16 (23.2%)	0.5
BMI on Index Day [mean (SD)]	20.2 (5.8)	18.3 (3.4)	0.048
Patients with Index HbA1c Value [n (%)]	283 (15.0%)	6 (8.7%)	0.15
HbA1c Value [mean (SD)]	11.6 (2.9)	12.9 (2.8)	0.29
Year of Diagnosis [n (%)]			
2008	305 (16.2%)	11 (15.9%)	0.46
2009	406 (21.5%)	15 (21.7%)	
2010	356 (18.9%)	20 (29.0%)	
2011	372 (19.7%)	9 (13.0%)	
2012	324 (17.2%)	10 (14.5%)	
2013	121 (6.4%)	4 (5.8%)	
Military branch [n (%)]			
Army	822 (43.6%)	31 (44.9%)	0.044
Coast Guard	39 (2.1%)	2 (2.9%)	
Air Force	471 (25.0%)	25 (36.2%)	
Marine Corps	134 (7.1%)	1 (1.4%)	
Navy	412 (21.9%)	9 (13.0%)	
Other	6 (0.3%)	1 (1.4%)	
Geographic region [n (%)]			
West	190 (10.1%)	3 (4.3%)	0.17
Central	293 (15.6%)	14 (20.3%)	
Northeast	678 (36.0%)	23 (33.3%)	
Southeast	595 (31.6%)	26 (37.7%)	
Alaska/Hawaii	80 (4.2%)	0 (0.0%)	
Non-US	48 (2.5%)	3 (4.3%)	
Rank of Sponsor [n (%)]			
Enlisted, Junior	124 (6.6%)	4 (5.8%)	0.028
Enlisted, Senior	1332 (70.7%)	41 (59.4%)	
Warrant Officer	59 (3.1%)	3 (4.3%)	
Officer, Junior	88 (4.7%)	3 (4.3%)	
Officer, Senior	281 (14.9%)	18 (26.1%)	
Emergency Care During 6-Month Baseline			
Patients with ER Visits [n (%)]	275 (14.6%)	2 (2.9%)	0.0041
ER Days [mean (SD)]	0.2 (0.6)	0.0 (0.2)	<0.0001
Patients with Hospitalization [n (%)]	19 (1.0%)	1 (1.4%)	0.51
Hospitalization Days [mean (SD)]	0.2 (4.5)	0.0 (0.4)	0.096
Emergency Care at T1DM Presentation			
Admitted to ER [n (%)]	1128 (59.9%)	28 (40.6%)	0.0014
Patients with Hospitalization [n (%)]	1244 (66.0%)	32 (46.4%)	0.0008
Hospitalization Days [mean (SD)]	2.5 (2.3)	2.3 (7.3)	0.85

Table 1 displays characteristics for patients with an index therapy of MDI compared to patients with an index therapy of CSII. The index therapy refers to the mode of insulin delivery being used three months after T1DM presentation. *We calculated statistical significance of continuous variables using a t-test and significance of binary and categorical variables using a chi square.

Table 2: Hospitalization Proportions by Age at Type 1 Diabetes Presentation (n=1,953).

Patient Age at T1DM Presentation (Years)	Number of Patients in Study (N=1,953)	Number Hospitalized at Presentation (N=1,276)	Proportion Hospitalized at Presentation
5	17	14	82.4%
6	38	31	81.6%
7	73	55	75.3%
8	122	96	78.7%
9	182	122	67.0%
10	191	144	75.4%
11	221	152	68.8%
12	177	123	69.5%
13	185	120	64.9%
14	161	103	64.0%
15	158	94	59.5%
16	150	86	57.3%
17	144	78	54.2%
18	134	58	43.3%

Table 3: Treatment patterns during follow-up (n=1,881).

Treatment Pattern	Patients* (N=1,881)
Switch to CSII only	494 (26.3%)
Augment with CGM only	43 (2.3%)
Switch and Augment within 90 days	137 (7.3%)
Switch before augment	120 (6.4%)
Augment before switch	19 (1.0%)
No treatment change	1,068 (56.8%)

*Patients using MDI three months after T1DM presentation.

Table 4: Patient characteristics by treatment change group (n=1,953).

Patient Characteristic	No Treatment Change (N=1,068)	Augment and/or Switch (N=813)	P-value*
Gender [n (%)]			
Female	432 (40.4%)	408 (50.2%)	<0.0001
Male	636 (59.6%)	405 (49.8%)	
Age on Index Day [mean (SD)]	13.0 (3.1)	11.6 (3.4)	<0.0001
Patients with Index BMI Value [n (%)]	291 (27.2%)	214 (26.3%)	0.65
Index BMI Value [mean (SD)]	21.9 (6.3)	17.8 (3.8)	<0.0001
Patients with Index HbA1c Value [n (%)]	172 (16.1%)	111 (13.7%)	0.14
Index HbA1c Value [mean (SD)]	11.5 (3.0)	11.8 (2.7)	0.47
Year of Diagnosis [n (%)]			
2008	137 (12.8%)	167 (20.5%)	<0.0001
2009	194 (18.2%)	212 (26.1%)	
2010	180 (16.9%)	176 (21.6%)	
2011	215 (20.1%)	157 (19.3%)	
2012	237 (22.2%)	85 (10.5%)	
2013	105 (9.8%)	16 (2.0%)	
Military branch [n (%)]			
Army	489 (45.8%)	332 (40.8%)	0.0084
Coast Guard	20 (1.9%)	19 (2.3%)	
Air Force	232 (21.7%)	237 (29.2%)	
Marine Corps	75 (7.0%)	59 (7.3%)	
Navy	248 (23.2%)	164 (20.2%)	
Other	4 (0.4%)	2 (0.2%)	
Geographic region [n (%)]			
West	116 (10.9%)	73 (9.0%)	0.0038
Central	141 (13.2%)	151 (18.6%)	
Northeast	378 (35.4%)	299 (36.8%)	
Southeast	366 (34.3%)	229 (28.2%)	
Alaska/Hawaii	40 (3.7%)	40 (4.9%)	
Non-US	27 (2.5%)	21 (2.6%)	
Rank of Sponsor [n (%)]			
Enlisted, Junior	77 (7.2%)	47 (5.8%)	<0.0001
Enlisted, Senior	804 (75.3%)	525 (64.6%)	
Warrant Officer	36 (3.4%)	23 (2.8%)	
Officer, Junior	39 (3.7%)	49 (6.0%)	
Officer, Senior	112 (10.5%)	169 (20.8%)	
Emergency Care During 6-Month Baseline			
Patients with ER Visits [n (%)]	168 (15.7%)	106 (13.0%)	0.1
ER Days [mean (SD)]	0.23 (0.7)	0.16 (0.5)	0.0082
Patients with Hospitalization [n (%)]	14 (1.3%)	4 (0.5%)	0.093
Hospitalization Days [mean (SD)]	0.4 (5.9)	0.0 (0.5)	0.063
Emergency Care at T1DM Presentation			
Admitted to ER [n (%)]	623 (58.3%)	504 (62.0%)	0.11
Patients with Hospitalization [n (%)]	676 (63.3%)	566 (69.6%)	0.0041
Hospitalization Days [mean (SD)]	2.4 (2.4)	2.5 (2.1)	0.44

Table 4 displays characteristics for patients who did not change treatment modality during follow compared to patients who initiated CSII and/or CGM. The index therapy refers to the mode of treatment being used three months after T1DM presentation. *We calculated statistical significance of continuous variables using a t-test and significance of binary and categorical variables using a chi square.

Table 5: Proportional Hazards Claims Analyses of Time to Initiation of CSII (n=1,953).

Patient Characteristic	Bivariate Analysis		Multivariate Claims Model		Final Claims Model	
	HR (95% C.L.)	P-value	HR (95% C.L.)	P-value	HR (95% C.L.)	P-value
Previous CGM Use	2.46 (1.79,3.39)	<.0001	2.40 (1.74, 3.31)	<.0001	2.40 (1.74, 3.30)	<.0001
Female Gender	1.35 (1.18,1.55)	<.0001	1.30 (1.13, 1.49)	0.0002	1.28 (1.12, 1.47)	0.0004
Age on Index Day	0.93 (0.91,0.95)	<.0001	0.94 (0.92, 0.96)	<.0001	0.94 (0.92, 0.96)	<.0001
Patients with Index BMI Value	1.09 (0.94,1.27)	0.27				
Index BMI Value	0.89 (0.86,0.92)	<.0001				
Patients with Index HbA1c Value	0.93 (0.76,1.13)	0.46				
Index HbA1c Value	1.05 (0.99, 1.12)	0.14				
Year of Diagnosis (p-value)		0.78				
2008	Ref.					
2009	1.02 (0.84, 1.25)	0.82				
2010	1.14 (0.92, 1.40)	0.24				
2011	1.02 (0.82, 1.28)	0.84				
2012	0.99 (0.76, 1.29)	0.94				
2013	1.23 (0.75, 2.03)	0.42				
Military branch (p-value)		0.03		0.02		
Navy	Ref.		Ref.			
Army	1.10 (0.92, 1.33)	0.30	1.10 (0.91, 1.34)	0.31		
Marine Corps	1.13 (0.83, 1.53)	0.44	1.01 (0.74, 1.37)	0.96		
Coast Guard	1.23 (0.77, 1.98)	0.39	1.05 (0.65, 1.70)	0.83		
Air Force	1.37 (1.13, 1.67)	0.002	1.24 (1.01, 1.52)	0.04		
Other	1.88 (0.60, 5.90)	0.28	1.14 (0.36, 3.62)	0.82		
Geographic region (p-value)		0.007		0.02		0.008
West	Ref.		Ref.		Ref.	
Southeast	1.04 (0.80, 1.35)	0.78	1.02 (0.78, 1.33)	0.89	1.06 (0.82, 1.38)	0.66
Alaska/Hawaii	1.09 (0.74, 1.61)	0.67	0.90 (0.61, 1.34)	0.61	0.93 (0.63, 1.38)	0.72
Non-US	1.17 (0.74, 1.86)	0.49	0.96 (0.60, 1.53)	0.85	1.01 (0.64, 1.61)	0.96
Northeast	1.22 (0.95, 1.58)	0.12	1.17 (0.91, 1.51)	0.23	1.17 (0.91, 1.51)	0.23
Central	1.51 (1.14, 1.99)	0.004	1.39 (1.04, 1.85)	0.02	1.49 (1.13, 1.96)	0.005
Rank of Sponsor (p-value)		<.0001		<.0001		<.0001
Enlisted, Junior	Ref.		Ref.		Ref.	
Enlisted, Senior	0.97 (0.73, 1.30)	0.84	0.97 (0.72, 1.31)	0.83	0.99 (0.74, 1.32)	0.93
Warrant Officer	1.02 (0.63, 1.67)	0.92	1.09 (0.67, 1.79)	0.73	1.10 (0.67, 1.80)	0.70
Officer, Junior	1.46 (0.99, 2.16)	0.06	1.33 (0.89, 1.98)	0.16	1.38 (0.93, 2.04)	0.11
Officer, Senior	1.84 (1.34, 2.53)	0.0002	1.72 (1.25, 2.39)	0.001	1.81 (1.32, 2.49)	0.0002
Emergency Care During 6-Month Baseline						
Patients with ER Visits	0.86 (0.70, 1.05)	0.13				
ER Days	0.86 (0.75, 0.99)	0.03	0.92 (0.80, 1.05)	0.22		
Patients with Hospitalization	0.58 (0.24, 1.39)	0.22				
Hospitalization Days	0.92 (0.83, 1.02)	0.11				
Emergency Care at T1DM Presentation						
Admitted to ER	1.08 (0.94, 1.24)	0.2778				
Patients with Hospitalization	1.27 (1.10, 1.47)	0.0014	1.16 (1.00, 1.35)	0.0566		
Hospitalization Days	1.02 (0.99, 1.05)	0.2078				

HR: Hazard Ratio

Table 6: Proportional Hazards Claims Analyses of Time to Initiation of CGM (n=1,953).

Patient Characteristic	Bivariate Analysis		Multivariate Claims Model		Final Claims Model	
	HR (95% C.L.)	P-value	HR (95% C.L.)	P-value	HR (95% C.L.)	P-value
Previous CSII Use	15.36 (12.39, 19.04)	<.0001	21.05 (16.62, 26.66)	<.0001	22.79 (18.13, 28.64)	<.0001
Female Gender	1.34 (1.09, 1.65)	0.006	1.15 (0.93, 1.44)	0.20		
Age on Index Day	0.96 (0.93, 0.99)	0.008	0.99 (0.96, 1.03)	0.72		
Patients with Index BMI Value	0.96 (0.75, 1.23)	0.76				
Index BMI Value	0.90 (0.86, 0.95)	0.0001				
Patients with Index HbA1c Value	0.68 (0.48, 0.97)	0.03	0.99 (0.96, 1.03)	0.32		
Index HbA1c Value	1.04 (0.93, 1.16)	0.53				
Year of Diagnosis (p-value)		0.0001		<.0001		<.0001
2008	Ref.		Ref.		Ref.	
2009	1.18 (0.86, 1.61)	0.32	1.53 (1.10, 2.13)	0.01	1.51 (1.10, 2.08)	0.01
2010	1.37 (0.97, 1.94)	0.08	2.20 (1.52, 3.19)	<.0001	2.23 (1.57, 3.18)	<.0001
2011	1.77 (1.22, 2.58)	0.003	4.78 (3.21, 7.14)	<.0001	4.73 (3.20, 6.99)	<.0001
2012	2.80 (1.81, 4.32)	<.0001	10.42 (6.49, 16.73)	<.0001	10.15 (6.41, 16.09)	<.0001
2013	2.36 (0.91, 6.10)	0.08	13.20 (4.93, 35.37)	<.0001	13.74 (5.16, 36.57)	<.0001
Military branch (p-value)		0.002		0.19		
Navy	Ref.		Ref.			
Army	1.23 (0.91, 1.67)	0.18	1.09 (0.79, 1.50)	0.59		
Marine Corps	1.91 (1.24, 2.94)	0.003	1.38 (0.89, 2.16)	0.15		
Coast Guard	2.47 (1.35, 4.50)	0.003	1.74 (0.933.23)	0.08		
Air Force	1.52 (1.11, 2.09)	0.01	1.06 (0.75, 1.50)	0.73		
Other	4.41 (1.08, 18.06)	0.04	3.69 (0.87, 15.60)	0.08		
Geographic region (p-value)		0.0005		0.22		
West	Ref.		Ref.			
Southeast	1.03 (0.68, 1.56)	0.90	1.06 (0.68, 1.64)	0.80		
Alaska/Hawaii	1.31 (0.73, 2.36)	0.37	1.01 (0.55, 1.85)	0.99		
Non-US	0.67 (0.28, 1.62)	0.38	0.65 (0.26, 1.62)	0.36		
Northeast	1.19 (0.79, 1.78)	0.41	1.08 (0.71, 1.65)	0.72		
Central	1.90 (1.24, 2.91)	0.003	1.44 (0.91, 2.27)	0.12		
Rank of Sponsor (p-value)		0.002		0.07		
Enlisted, Junior	Ref.		Ref.			
Enlisted, Senior	1.06 (0.66, 1.72)	0.80	1.11 (0.67, 1.82)	0.69		
Warrant Officer	1.56 (0.78, 3.13)	0.21	1.58 (0.78, 3.22)	0.21		
Officer, Junior	1.47 (0.79, 2.75)	0.22	1.43 (0.75, 2.72)	0.28		
Officer, Senior	1.79 (1.07, 2.99)	0.03	1.57 (0.92, 2.71)	0.10		
Emergency Care During 6-Month Baseline						
Patients with ER Visits	0.79 (0.56, 1.10)	0.16				
ER Days	0.86 (0.69, 1.08)	0.20				
Patients with Hospitalization	0.98 (0.32, 3.06)	0.97				
Hospitalization Days	0.97 (0.87, 1.07)	0.52				
Emergency Care at T1DM Presentation						
Admitted to ER	1.07 (0.87, 1.33)	0.52				
Patients with Hospitalization	1.15 (0.92, 1.44)	0.22				
Hospitalization Days	1.02 (0.99, 1.05)	0.28				

HR: Hazard Ratio

Table 7: CSII Restricted Cox PH Claims Analyses of Time to Treatment Change (n=820).

Patient Characteristic	Bivariate Analysis		Multivariate Claims Analysis	
	HR (95% C.L.)	P-value	HR (95% C.L.)	P-value
Female Gender	1.07 (0.85,1.34)	0.56		
Age on Index Day	1.02 (0.99, 1.05)	0.28		
Patients with Index BMI Value	1.02 (0.79,1.33)	0.86		
Index BMI Value	0.99 (0.94, 1.05)	0.80		
Patients with Index HbA1c Value	0.75 (0.52, 1.09)	0.13		
Index HbA1c Value	1.04 (0.92, 1.17)	0.58		
Year of Diagnosis (p-value)		<.0001		<.0001
2008	Ref.		Ref.	
2009	1.25 (0.90, 1.75)	0.19	1.21 (0.86, 1.70)	0.27
2010	1.46 (1.01, 2.11)	0.04	1.34 (0.92, 1.94)	0.13
2011	2.39 (1.61, 3.55)	<.0001	2.37 (1.59, 3.53)	<.0001
2012	5.49 (3.45, 8.75)	<.0001	5.51 (3.44, 8.81)	<.0001
2013	5.03 (1.53, 16.58)	0.008	4.87 (1.47, 16.09)	0.009
Military branch (p-value)		0.009		0.005
Navy	Ref.		Ref.	
Army	1.22 (0.88, 1.69)	0.24	1.09 (0.77, 1.52)	0.64
Marine Corps	1.94 (1.22, 3.07)	0.005	1.89 (1.19, 3.00)	0.008
Coast Guard	2.44 (1.27, 4.68)	0.007	2.39 (1.24, 4.61)	0.009
Air Force	1.28 (0.91, 1.80)	0.16	1.15 (0.81, 1.65)	0.44
Other	4.10 (1.00, 16.85)	0.05	4.44 (1.06, 18.65)	0.041
Geographic region (p-value)		0.05		0.05
West	Ref.		Ref.	
Southeast	0.89 (0.57, 1.39)	0.61	0.98 (0.62, 1.55)	0.94
Alaska/Hawaii	1.05 (0.56, 1.95)	0.89	1.14 (0.61, 2.15)	0.68
Non-US	0.58 (0.24, 1.41)	0.23	0.66 (0.27, 1.63)	0.37
Northeast	1.00 (0.65, 1.54)	0.99	1.12 (0.72, 1.72)	0.62
Central	1.42 (0.91, 2.22)	0.13	1.58 (0.99, 2.52)	0.06
Rank of Sponsor (p-value)		0.66		
Enlisted, Junior	Ref.			
Enlisted, Senior	1.04 (0.62, 1.73)	0.88		
Warrant Officer	1.43 (0.68, 3.02)	0.35		
Officer, Junior	1.22 (0.64, 2.33)	0.55		
Officer, Senior	1.21 (0.70, 2.09)	0.49		
Emergency Care During 6-Month Baseline				
Patients with ER Visits	0.98 (0.70, 1.37)	0.90		
ER Days	1.06 (0.83, 1.35)	0.65		
Patients with Hospitalization	1.71 (0.55, 5.34)	0.35		
Hospitalization Days	1.13 (0.95, 1.34)	0.16		
Emergency Care at T1DM Presentation				
Admitted to ER	1.03 (0.82, 1.30)	0.80		
Patients with Hospitalization	1.03 (0.81, 1.32)	0.79		
Hospitalization Days	1.01 (0.99, 1.04)	0.35		

HR: Hazard Ratio

Table 8: Cox Proportional Hazards EMR Analyses of Time to Initiation of CSII (n=521).

Patient Characteristic	Multivariate EMR Model		Final EMR Model	
	HR (95% C.L.)	P-value	HR (95% C.L.)	P-value
Previous CGM Use	1.85 (0.67,5.08)	0.24		
Female Gender	1.23 (0.94, 1.62)	0.13		
Age on Index Day	0.96 (0.91, 1.00)	0.05		
Patients with Index BMI Value				
Index BMI Value	0.91 (0.88, 0.95)	<.0001	0.89 (0.86, 0.92)	<.0001
Patients with Index HbA1c Value	1.85 (0.67, 5.08)	0.24		
Index HbA1c Value				
Year of Diagnosis (p-value)				
2008				
2009				
2010				
2011				
2012				
2013				
Military branch (p-value)		0.18		
Navy	Ref.			
Army	0.81 (0.56, 1.18)	0.28		
Marine Corps	0.57 (0.29, 1.10)	0.09		
Coast Guard	0.21 (0.03, 1.58)	0.13		
Air Force	1.07 (0.73, 1.56)	0.75		
Other	0.86 (0.19, 3.84)	0.84		
Geographic region (p-value)		0.03		0.01
West	Ref.		Ref.	
Southeast	0.76 (0.46, 1.25)	0.28	0.88 (0.55, 1.41)	0.59
Alaska/Hawaii	0.75 (0.40, 1.41)	0.37	0.81 (0.44, 1.50)	0.51
Non-US	0.67 (0.27, 1.66)	0.39	0.73 (0.30, 1.79)	0.49
Northeast	0.76 (0.47, 1.23)	0.26	0.84 (0.53, 1.33)	0.45
Central	1.41 (0.83, 2.39)	0.21	1.62 (0.99, 2.65)	0.05
Rank of Sponsor (p-value)		0.006		0.002
Enlisted, Junior	Ref.		Ref.	
Enlisted, Senior	1.10 (0.44, 2.74)	0.84	1.23 (0.50, 3.02)	0.65
Warrant Officer	1.66 (0.56, 4.92)	0.36	1.66 (0.57, 4.89)	0.35
Officer, Junior	2.01 (0.73, 5.57)	0.18	2.16 (0.79, 5.86)	0.13
Officer, Senior	2.13 (0.84, 5.43)	0.11	2.24 (0.90, 5.60)	0.08
Emergency Care During 6-Month Baseline				
Patients with ER Visits				
ER Days	0.93 (0.71, 1.22)	0.60		
Patients with Hospitalization				
Hospitalization Days				
Emergency Care at T1DM Presentation				
Admitted to ER				
Patients with Hospitalization	1.13 (0.81,1.56)	0.47		
Hospitalization Days				

HR: Hazard Ratio

Table 9: Cox Proportional Hazards EMR Analyses of Time to Initiation of CGM (n=521).

Patient Characteristic	Multivariate EMR Model		Final EMR Model	
	HR (95% C.L.)	P-value	HR (95% C.L.)	P-value
Previous CSII Use	25.61 (15.02, 43.66)	<.0001	27.00 (16.47, 44.28)	<.0001
Female Gender	1.20 (0.75, 1.92)	0.46		
Age on Index Day	1.01 (0.92, 1.10)	0.85		
Patients with Index BMI Value				
Index BMI Value	0.93 (0.87, 1.00)	0.05	0.94 (0.890.99)	0.03
Patients with Index HbA1c Value	0.85 (0.51, 1.43)	0.55		
Index HbA1c Value				
Year of Diagnosis (p-value)		<.0001		<.0001
2008	Ref.		Ref.	
2009	2.37 (0.31, 18.00)	0.40	2.40 (0.32, 17.89)	0.39
2010	2.29 (0.29, 17.93)	0.43	3.08 (0.41, 23.33)	0.28
2011	7.29 (0.93, 56.97)	0.06	7.26 (0.95, 55.38)	0.06
2012	27.49 (3.38, 223.81)	0.002	27.46 (3.50, 215.47)	0.002
2013	14.34 (0.83, 248.01)	0.07	14.30 (0.85, 241.93)	0.07
Military branch (p-value)	Not Enough Data		Not Enough Data	
Navy				
Army				
Marine Corps				
Coast Guard				
Air Force				
Other				
Geographic region (p-value)		0.65		
West	Ref.			
Southeast	0.91 (0.40, 2.06)	0.82		
Alaska/Hawaii	0.68 (0.25, 1.85)	0.45		
Non-US	0.31 (0.04, 2.51)	0.27		
Northeast	0.86 (0.38, 1.95)	0.72		
Central	1.27 (0.57, 2.82)	0.56		
Rank of Sponsor (p-value)		0.17		
Enlisted, Junior	Ref.			
Enlisted, Senior	0.36 (0.12, 1.10)	0.07		
Warrant Officer	0.38 (0.08, 1.89)	0.24		
Officer, Junior	0.58 (0.16, 2.06)	0.40		
Officer, Senior	0.63 (0.20, 1.99)	0.43		
Emergency Care During 6-Month Baseline				
Patients with ER Visits				
ER Days				
Patients with Hospitalization				
Hospitalization Days				
Emergency Care at T1DM Presentation				
Admitted to ER				
Patients with Hospitalization				
Hospitalization Days				

HR: Hazard Ratio

Figures

Figure 1: Diagram of patient selection and treatment patterns.

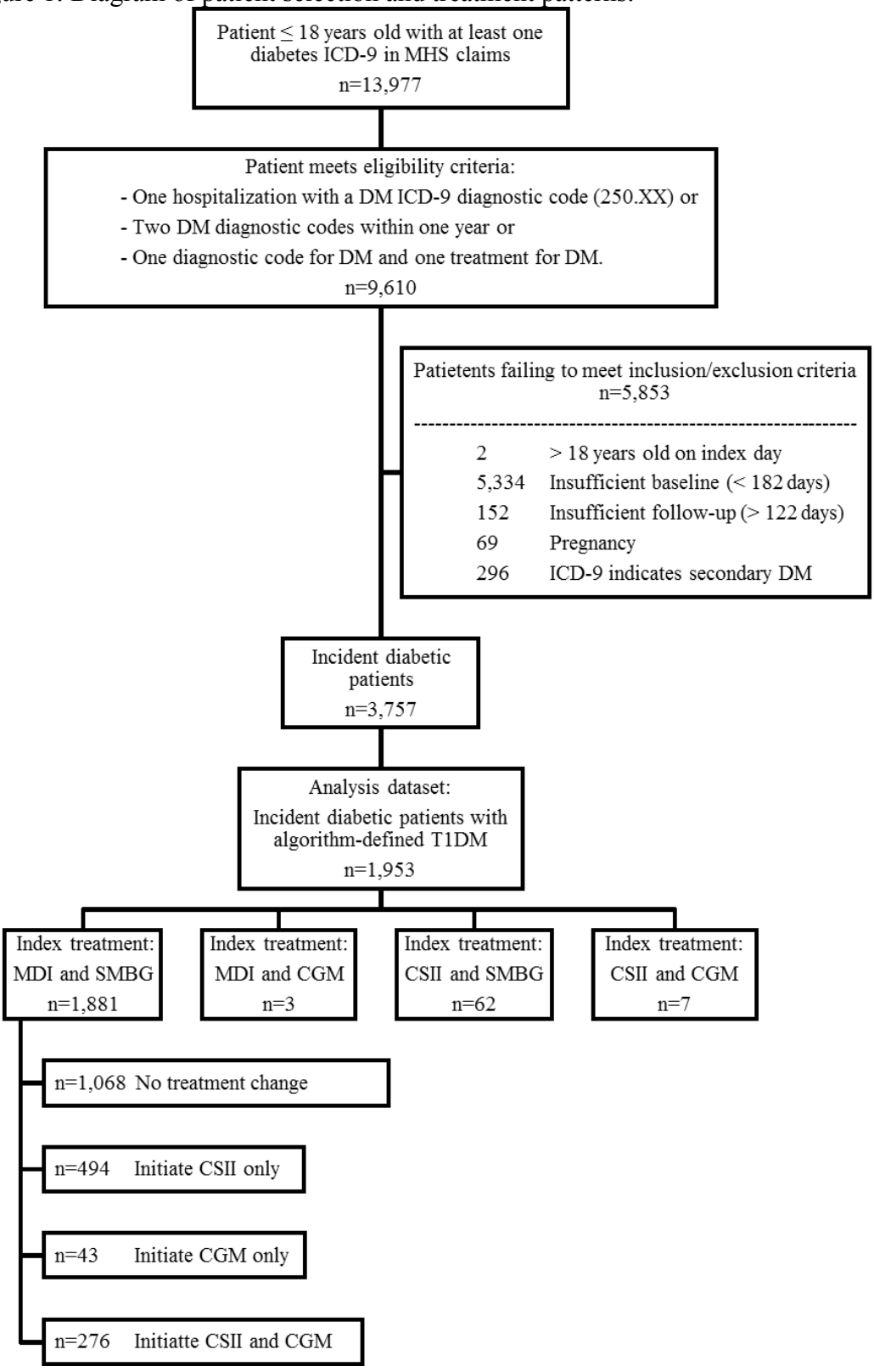

Figure 2: Study population average hemoglobin A1c by year of follow-up (n=1,953).

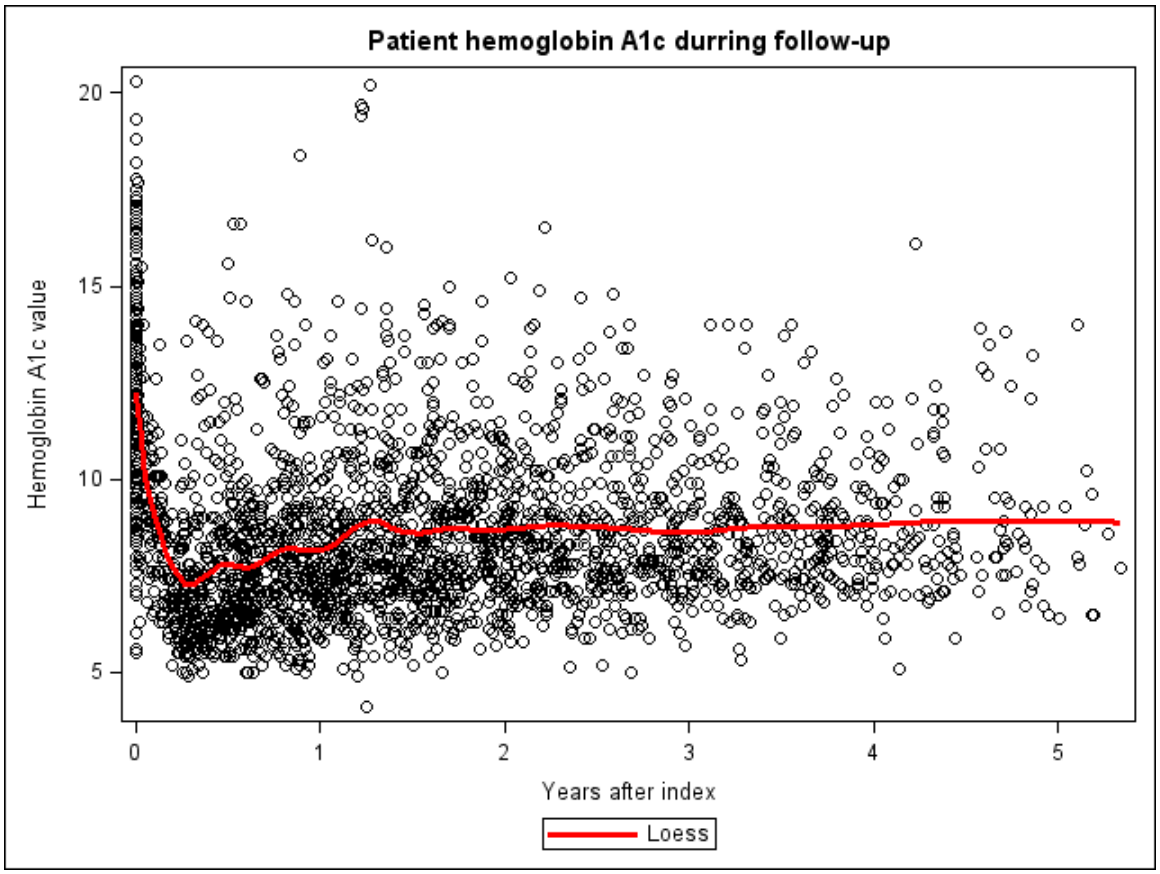

Figure 2 displays a Lowess plot of the study population average hemoglobin A1c during follow-up (years). The effect of the "honeymoon period" is demonstrated by the characteristic improvement in glycemic control 3 months after presentation followed by a steady increase in hemoglobin A1c until approximately one year after diagnosis.

Figure 3: Kaplan Meier plot of time to CSII initiation (n=1,953).

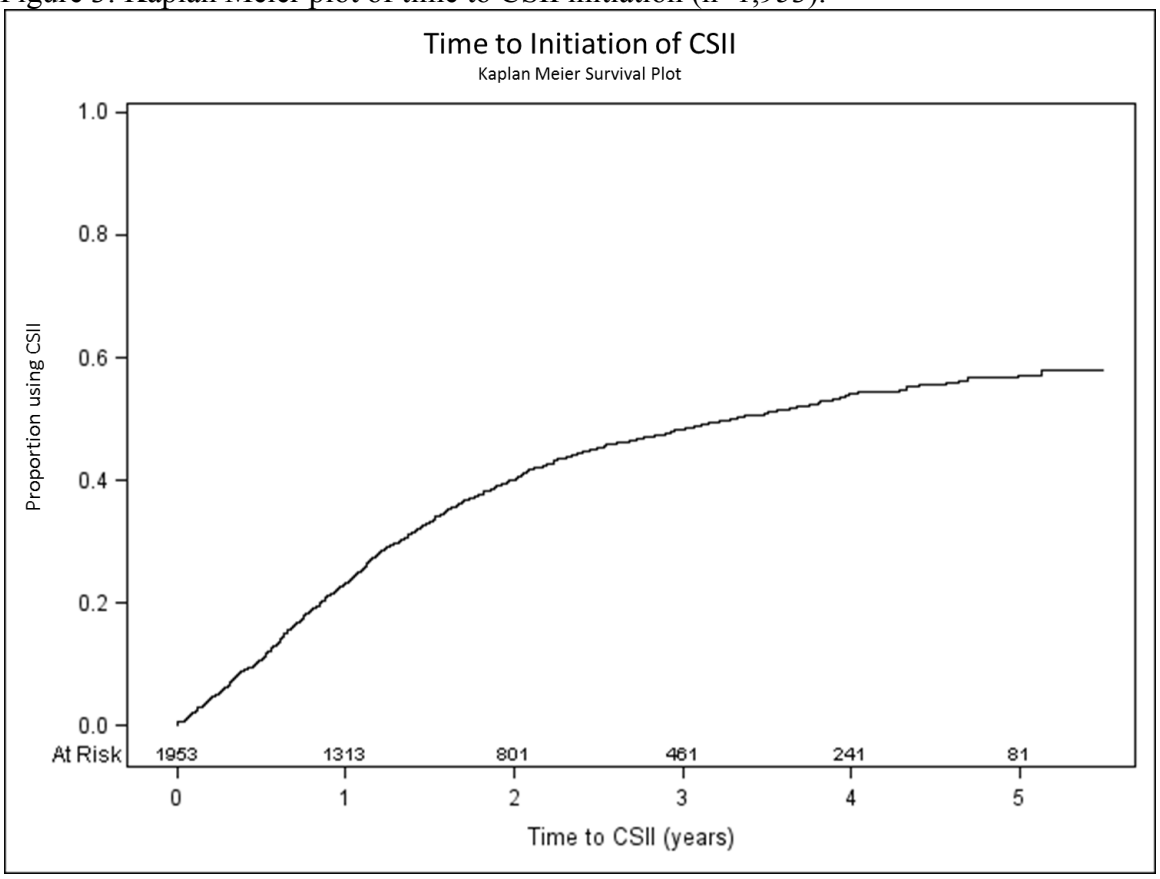

Figure 3 displays a Kaplan Meier plot of the cumulative proportion of patients initiating continuous subcutaneous insulin infusion (CSII) and the risk set at each year during follow-up.

Figure 4: Kaplan Meier plot of time to CGM initiation (n=1,953).

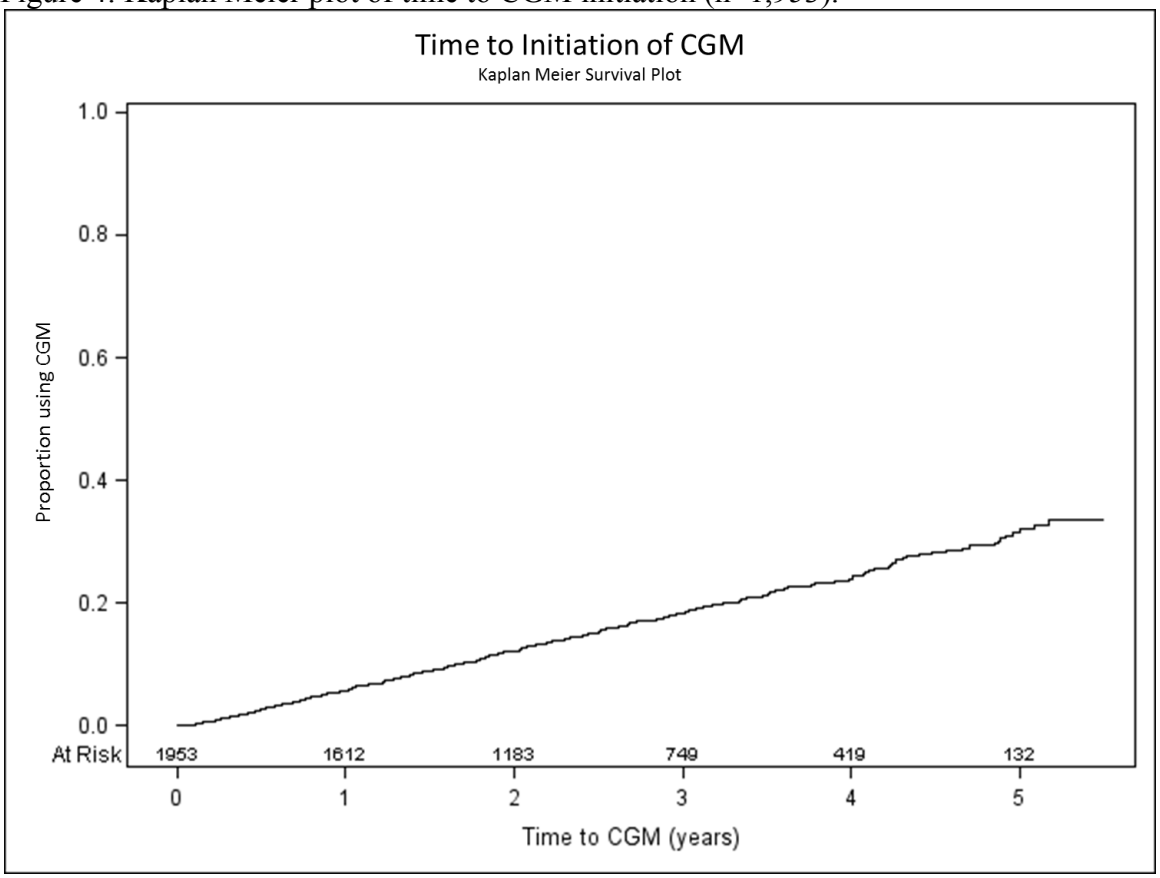

Figure 4 displays a Kaplan Meier plot of the cumulative proportion of patients initiating continuous glucose monitoring (CGM) and the risk set at each year during follow-up.

Figure 5: Kaplan Meier plot of time CSII initiation by gender (n=1,953).

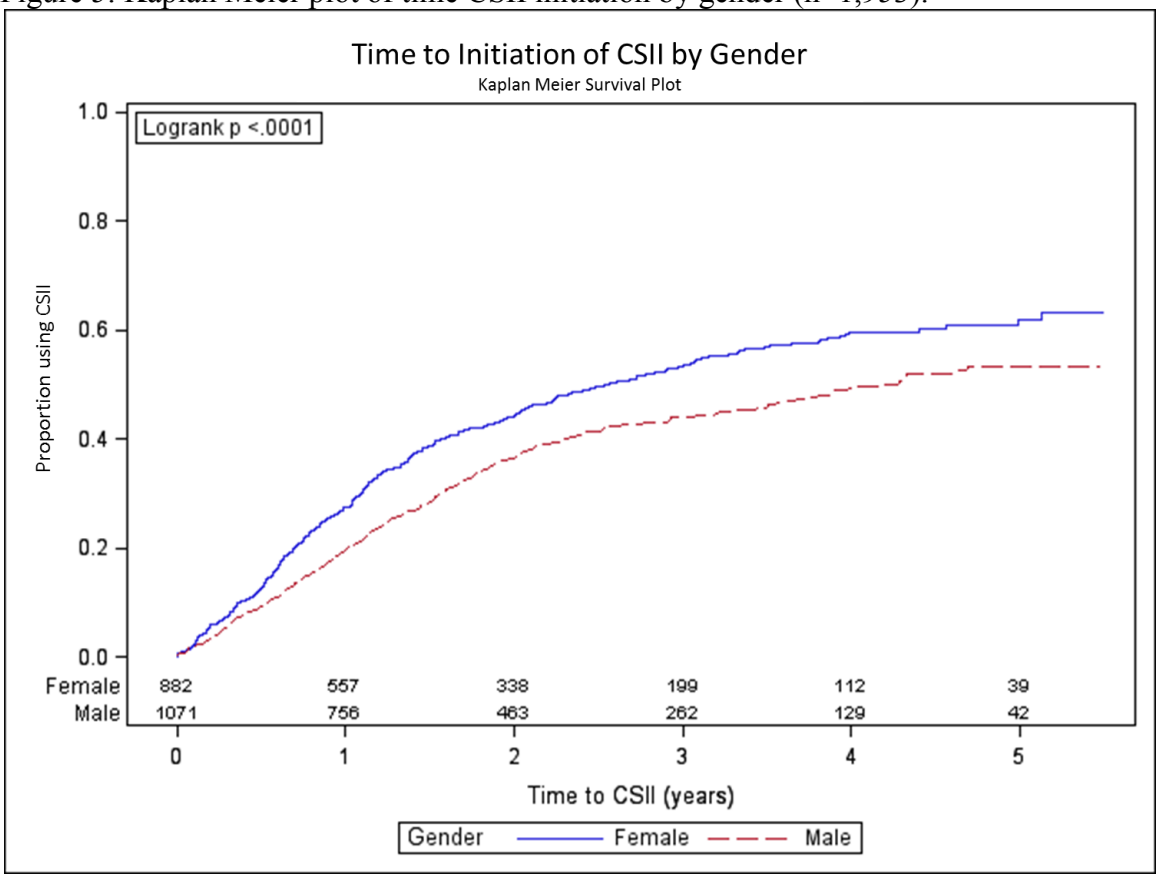

Figure 5 displays a Kaplan Meier plot of the cumulative proportion of patients initiating continuous subcutaneous insulin infusion (CSII) by gender and the risk set at each year during follow-up. We calculated statistical significance of the difference in the proportion of males and females initiating CSII using a Log-Rank test.

Figure 6: Kaplan Meier plot of time to CGM initiation by gender (n=1,953).

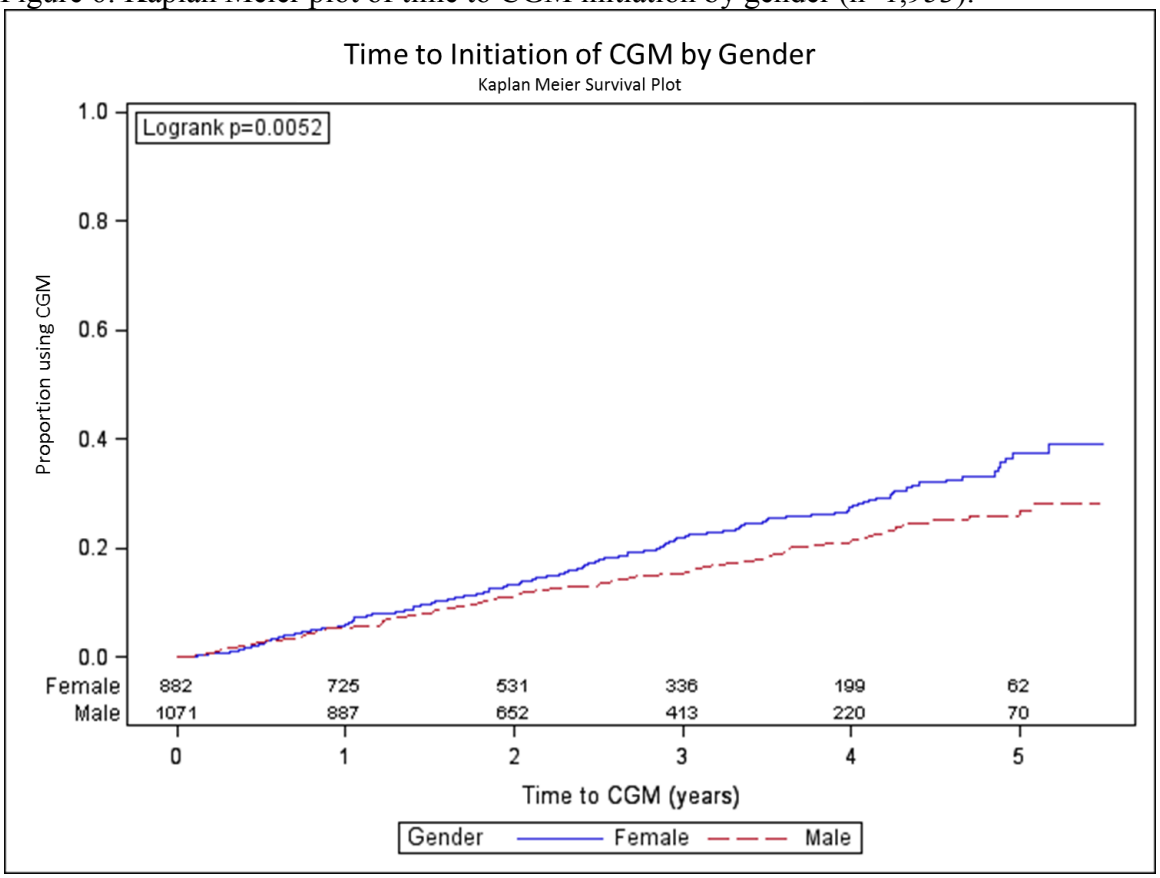

Figure 6 displays a Kaplan Meier plot of the cumulative proportion of patients initiating continuous glucose monitoring (CGM) by gender and the risk set at each year during follow-up. We calculated statistical significance of the difference in the proportion of males and females initiating CGM using a Log-Rank test.

Figure 7: Kaplan Meier plot of time from CSII to CGM initiation by gender (n=790).

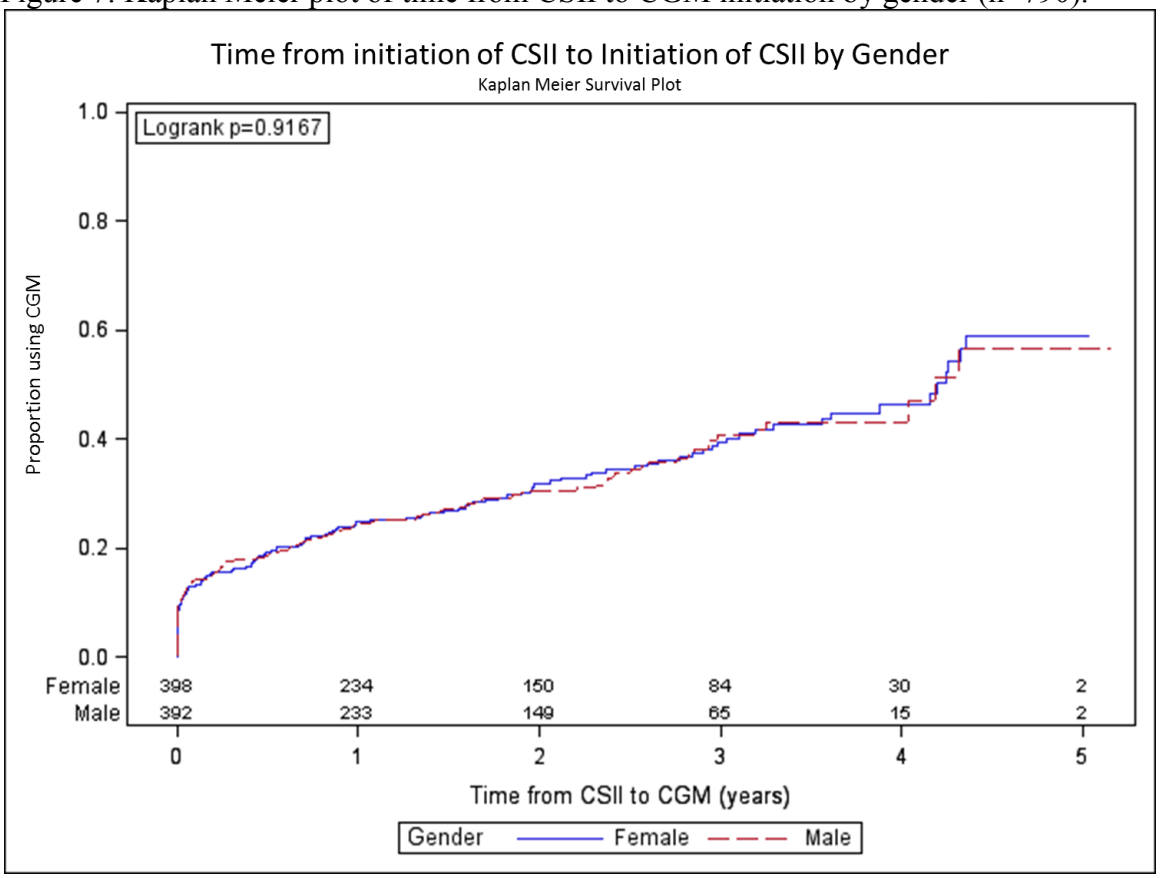

Figure 7 displays a Kaplan Meier plot of the cumulative proportion of patients initiating continuous glucose monitoring (CGM) by gender and the risk set at each year during follow-up. All patients included in this analysis had previously initiated continuous subcutaneous insulin infusion (CSII). We calculated statistical significance of the difference in the proportion of males and females initiating CGM using a Log-Rank test.

Figure 8: Kaplan Meier plot of time to CSII initiation by year of diagnosis (n=1,953).

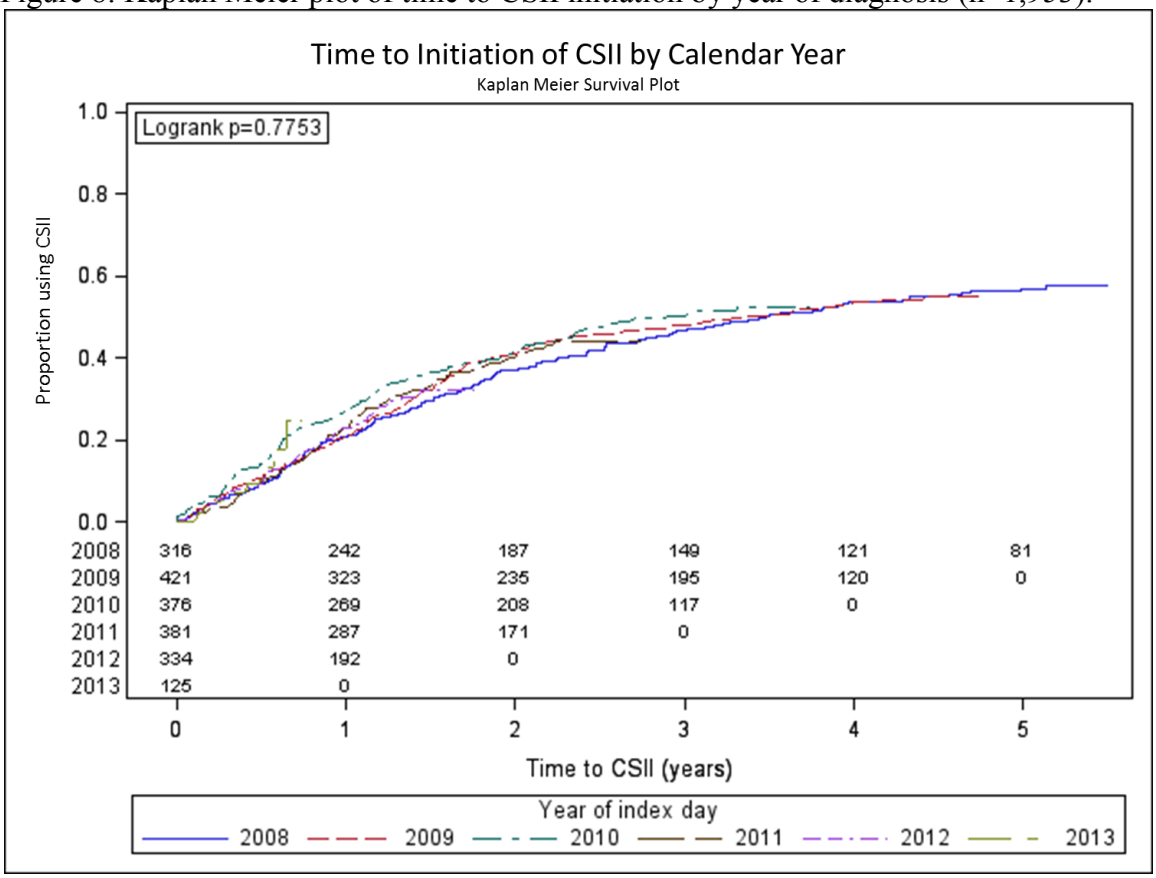

Figure 8 displays a Kaplan Meier plot of the cumulative proportion of patients initiating continuous subcutaneous insulin infusion (CSII) by calendar year of T1DM presentation and the risk set at each year during follow-up. We calculated statistical significance of the difference in the proportion of patients initiating CSII during each year using a Log-Rank test.

Figure 9: Kaplan Meier plot of time to CGM initiation by year of diagnosis (n=1,953).

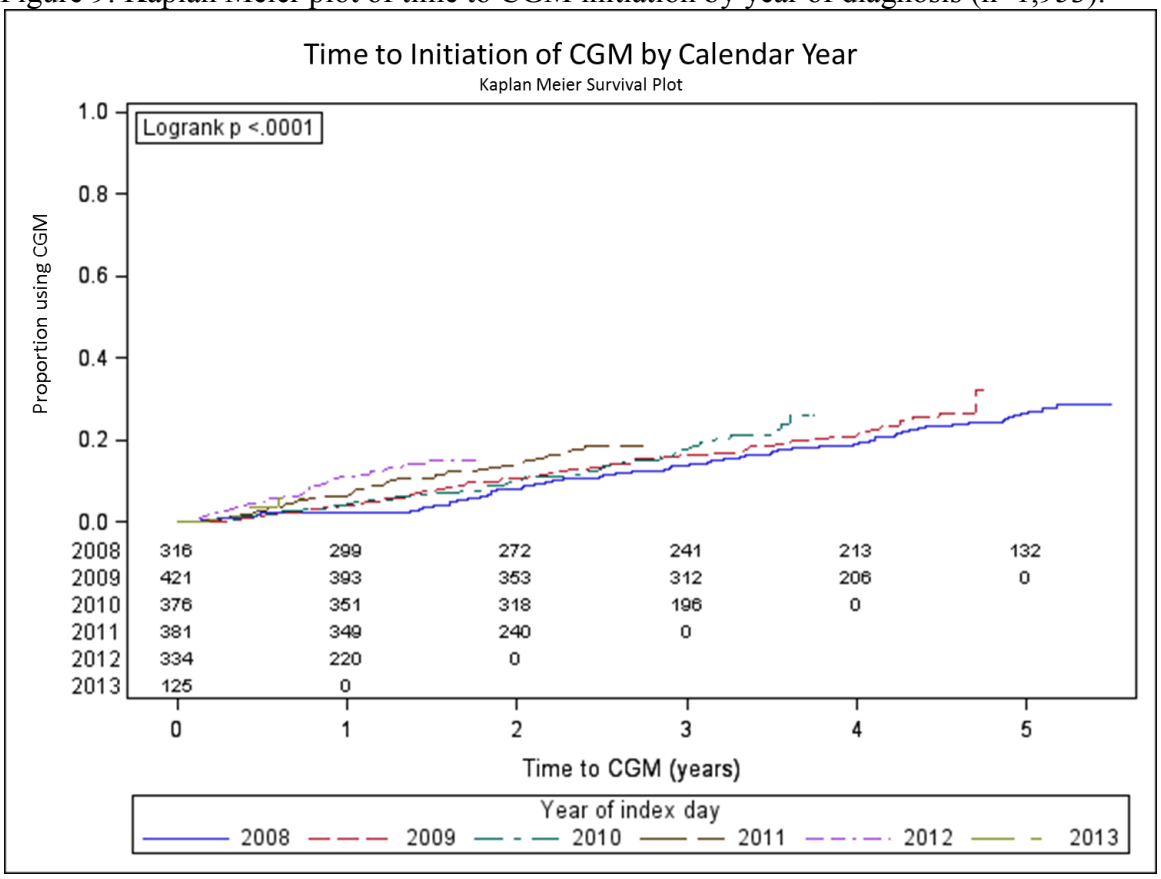

Figure 9 displays a Kaplan Meier plot of the cumulative proportion of patients initiating continuous glucose monitoring (CGM) by calendar year of T1DM presentation and the risk set at each year during follow-up. We calculated statistical significance of the difference in the proportion of patients initiating CGM during each year using a Log-Rank test.

Appendix Tables

Table A1: Patient Attrition.

Inclusion/Exclusion Criteria	Patients Remaining	Patients Excluded
Patient has a DM Dx	13,977 (100.0%)	
Patient has sufficient DM Dx/med criteria	9,610 (68.8%)	4,367 (31.2%)
Patient was less than 19 years old at the time of first diagnosis	9,608 (68.7%)	2 (0.0%)
Patient has sufficient baseline (182 days) enrollment	4,274 (30.6%)	5,334 (38.2%)
Patient has sufficient follow-up (122 days) enrollment	4,122 (29.5%)	152 (1.1%)
Patient not excluded for pregnancy	4,053 (29.0%)	69 (0.5%)
Patient not excluded for condition Dx	3,757 (26.9%)	296 (2.1%)
Patient has algorithm defined T1DM	1,953 (14.0%)	1,804 (12.9%)

Appendix Table 1 displays the number of patients excluded and the number of patient remaining after each inclusion/exclusion criteria. These data are also displayed in Figure 1.

Table A2: Patient Characteristics by Index Treatment Group (n=1,953).

Patient Characteristic	All Patients (N=1,953)	MDI and SMBG (N=1,881)	MDI and CGM (N=3)	CSII and SMBG (N=62)	CSII and CGM (N=7)
Gender [n (%)]					
Female	882 (45.2%)	840 (44.7%)	2 (66.7%)	37 (59.7%)	3 (42.9%)
Male	1071 (54.8%)	1041 (55.3%)	1 (33.3%)	25 (40.3%)	4 (57.1%)
Age on Index Day [mean (SD)]	12.4 (3.3)	12.4 (3.3)	10.3 (1.5)	12.7 (3.8)	16.3 (3.3)
Patients with Index BMI Value [n (%)]	521 (26.7%)	505 (26.8%)	0 (0.0%)	12 (19.4%)	4 (57.1%)
BMI Value [mean (SD)]	20.1 (5.7)	20.2 (5.8)	NA	18.3 (3.4)	18.4 (4.1)
Patients with Index HbA1c Value [n (%)]	289 (14.8%)	283 (15.0%)	0 (0.0%)	6 (9.7%)	0 (0.0%)
HbA1c Value [mean (SD)]	11.6 (2.9)	11.6 (2.9)	NA	12.9 (2.8)	NA
Year of Diagnosis [n (%)]					
2008	316 (16.2%)	304 (16.2%)	1 (33.3%)	10 (16.1%)	1 (14.3%)
2009	421 (21.6%)	406 (21.6%)	0 (0.0%)	14 (22.6%)	1 (14.3%)
2010	376 (19.3%)	356 (18.9%)	0 (0.0%)	19 (30.6%)	1 (14.3%)
2011	381 (19.5%)	372 (19.8%)	0 (0.0%)	8 (12.9%)	1 (14.3%)
2012	334 (17.1%)	322 (17.1%)	2 (66.7%)	7 (11.3%)	3 (42.9%)
2013	125 (6.4%)	121 (6.4%)	0 (0.0%)	4 (6.5%)	0 (0.0%)
Military branch [n (%)]					
Army	853 (43.7%)	821 (43.6%)	1 (33.3%)	29 (46.8%)	2 (28.6%)
Coast Guard	41 (2.1%)	39 (2.1%)	0 (0.0%)	1 (1.6%)	1 (14.3%)
Air Force	496 (25.4%)	469 (24.9%)	2 (66.7%)	23 (37.1%)	2 (28.6%)
Marine Corps	135 (6.9%)	134 (7.1%)	0 (0.0%)	1 (1.6%)	0 (0.0%)
Navy	421 (21.6%)	412 (21.9%)	0 (0.0%)	8 (12.9%)	1 (14.3%)
Other	7 (0.4%)	6 (0.3%)	0 (0.0%)	0 (0.0%)	1 (14.3%)
Geographic region [n (%)]					
West	193 (9.9%)	189 (10.0%)	1 (33.3%)	1 (1.6%)	2 (28.6%)
Central	307 (15.7%)	292 (15.5%)	1 (33.3%)	13 (21.0%)	1 (14.3%)
Northeast	701 (35.9%)	677 (36.0%)	1 (33.3%)	23 (37.1%)	0 (0.0%)
Southeast	621 (31.8%)	595 (31.6%)	0 (0.0%)	22 (35.5%)	4 (57.1%)
Alaska/Hawaii	80 (4.1%)	80 (4.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Non-US	51 (2.6%)	48 (2.6%)	0 (0.0%)	3 (4.8%)	0 (0.0%)
Rank of Sponsor [n (%)]					
Enlisted, Junior	128 (6.6%)	124 (6.6%)	0 (0.0%)	4 (6.5%)	0 (0.0%)
Enlisted, Senior	1373 (70.3%)	1329 (70.7%)	3 (100.0%)	37 (59.7%)	4 (57.1%)
Warrant Officer	62 (3.2%)	59 (3.1%)	0 (0.0%)	2 (3.2%)	1 (14.3%)
Officer, Junior	91 (4.7%)	88 (4.7%)	0 (0.0%)	3 (4.8%)	0 (0.0%)
Officer, Senior	299 (15.3%)	281 (14.9%)	0 (0.0%)	16 (25.8%)	2 (28.6%)
Emergency Care During 6-Month Baseline					
Patients with ER Visits [n (%)]	277 (14.2%)	274 (14.6%)	1 (33.3%)	2 (3.2%)	0 (0.0%)
ER Days [mean (SD)]	0.2 (0.6)	0.2 (0.6)	1.0 (1.7)	0.0 (0.2)	0.0 (0.0)
Patients with Hospitalization [n (%)]	20 (1.0%)	18 (1.0%)	1 (33.3%)	1 (1.6%)	0 (0.0%)
Hospitalization Days [mean (SD)]	0.2 (4.4)	0.2 (4.5)	4.3 (7.5)	0.0 (0.4)	0.0 (0.0)
Emergency Care at T1DM Presentation					
Admitted to ER [n (%)]	1156 (59.2%)	1127 (59.9%)	1 (33.3%)	22 (35.5%)	6 (85.7%)
Patients with Hospitalization [n (%)]	1276 (65.3%)	1242 (66.0%)	2 (66.7%)	27 (43.5%)	5 (71.4%)
Hospitalization Days [mean (SD)]	2.5 (2.6)	2.5 (2.3)	2.0 (1.7)	2.3 (7.7)	2.1 (1.6)

Appendix Table 2 displays patient characteristics for all patients and by index treatment group. The index therapy refers to the mode of insulin delivery being used three months after T1DM presentation.

CHAPTER 3: MANUSCRIPT 2 – GLYCEMIC CONTROL

Abstract

Purpose: The purpose of this study was to estimate the effects of initiating continuous subcutaneous insulin infusion (CSII) and/or a continuous glucose monitor (CGM) on hemoglobin A1c in an observational cohort of pediatric patients with type 1 diabetes mellitus (T1DM).

Methods: This study was performed using data extracted from the US Department of Defense (DOD) Military Health Systems (MHS) database between October 2007 and September 2013. Exploratory analyses were performed to develop an algorithm designed to identify diabetic patients and differentiate between type 1 and type 2 diabetes. We created a mixed effects model to estimate the effects of switching insulin delivery method from multiple daily injections (MDI) to continuous subcutaneous insulin infusion (CSII) and/or augmenting treatment with a continuous glucose monitor (CGM) on hemoglobin A1c.

Results: We identified 1,318 pediatric patients with T1DM. We observed 174 treatment switches and 159 augments, including 24 occurrences where a switch and augment occurred in the same time period. Changes in hemoglobin A1c after a treatment change depended on the initial hemoglobin A1c. We found patients with an initial A1c of 6% did not experience improved glycemic control from a treatment change. However, a patient with an initial A1c of 9% would experience a reduction of 0.55% ($p<0.0001$) from a switch and 0.30% ($p=0.002$) from an augment, and a patient with a hemoglobin A1c of 12% would experience a reduction of 1.13% ($p<0.0001$) from a switch and 0.51% ($p=0.007$) from an augment.

Conclusion: Many patients in our cohort demonstrated clinically meaningful reductions in hemoglobin A1c after initiating CSII and/or CGM.

Introduction

Tight glycemic control is required to reduce the risk of complications from type 1 diabetes mellitus (T1DM). Poor glycemic control in adolescence is associated with impaired cognitive function in adulthood.[1,2,3] Repeated episodes of severe hypoglycemia (SH) can lead to seizures, cardiovascular disease, and cognitive decline.[4] Long term consequences of chronic hyperglycemia include: retinopathy[5], neuropathy[6], digestive disorders[7], cardiovascular disease[8], and kidney disease.[9] An absolute reduction in hemoglobin A1c of 0.5% is considered to be clinically meaningful because this level of increased glycemic control results in significant reductions in chronic microvascular complications such as nephropathy and retinopathy.[10,11,12,13]

Continuous subcutaneous insulin infusion (CSII), also known as an insulin pump, more closely imitates the body's natural metabolic processes compared to multiple daily injections (MDI). A continuous glucose monitor (CGM) is a device that provides a glucose reading every few minutes so that patients may more easily recognize patterns and trends over time. In theory, these treatments should improve a patient's glycemic control. However, clinical trials measuring the effects of CSII and/or CGM usage compared to conventional therapy, which consists of MDI and self-monitoring of blood glucose (SMBG) through finger sticks, on glycemic control have demonstrated mixed results. A recent systematic review comparing MDI with CSII found no statistically significant difference in hemoglobin A1c levels in children, though adults' hemoglobin A1c levels were on average 0.3% lower with CSII.[14] Clinical trials of CGM in children have generally not demonstrated clinically meaningful differences in glycemic control

except in those with strict adherence or the highest hemoglobin A1c levels at baseline.[15,16,17]

In clinical trials, treatment groups are assigned. However, treatment choices in the real world are non-random and motivated by many factors. Consequently changes in glycemic control after initiation of CSII or CGM observed by patients participating in clinical trials may be different than what patients experience in typical care setting. In this study, we aimed to estimate changes in hemoglobin A1c associated with a change in treatment (initiation of CSII and/or CGM) in an observational cohort of pediatric patients with type 1 diabetes.

Methods

Study Population

This study was performed using data extracted from the US Department of Defense (DOD) Military Health Systems (MHS) database. The DOD MHS serves active and past military personnel (known as the sponsor) and their dependents. The database includes both an electronic medical record (EMR) and a medical insurance claims component. All patients are included in the insurance claims data, and approximately one third have EMR data. Data collected includes: demographics, diagnostic codes, information on medical procedures, symptoms, vital signs, laboratory and radiology results, and pharmacy orders and claims. The crude data, prepared by Health Research Tx (HRTx), included all EMR encounters and insurance claims for patients with at least one International Classification of Diseases, Ninth Revision (ICD-9) diagnostic code indicating diabetes (250.XX) before their 19th birthday. All personal identifiable

information was removed. At the time of extraction, data were available between October 2007 and September 2013.

Patients in the DOD MHS dataset during the study period meeting the following criteria were selected for this study:

- At least one of the following:
    - One hospitalization with an ICD-9 diagnostic code for DM (250.XX)
    - Two DM diagnostic codes within one year
    - One diagnostic code for DM and one treatment for DM
- Patient has algorithm defined type 1 diabetes
- Age 18 years or younger at first diabetes diagnosis
- A minimum of 16 months of enrollment after first DM diagnosis
- A minimum of 2 hemoglobin A1c measurements occurring more than one year after first diabetes diagnosis date

Previous studies, [18,19] as well as our own exploratory analyses, have shown that glycemic control varies drastically during the first year after type 1 diabetes diagnosis. Because we could not perfectly distinguish between incident and prevalent diabetes, we required a 12 month baseline period after the first indication of T1DM in the data, and no outcomes were measured until completion of the baseline period. Among patients meeting the eligibility criteria, the first day after the completion of the baseline period was considered the index day for the study. We also required at minimum of 4 months of follow-up. These requirements enabled us to create cohort with established, and thus, more stable diabetes and with enough follow-up to measure study outcomes (time for two or more hemoglobin A1c measurements).

Exclusion criteria were chosen to reduce the number of patients with gestational or other secondary (non-type 1 or 2) diabetes. Patients also needed to be at risk of changing treatment during follow-up. Patients meeting the following criteria were excluded from the study:

- Patients becoming pregnant less than four months after index date were excluded. (Patients becoming pregnant greater than four months after index were censored at the pregnancy date.)
- Patients with an ICD-9 code indicating any of the following: secondary diabetes (249.x), other endocrine dysfunction (251.8), adrenal cortical steroids causing adverse effects in therapeutic use (E932.0), adenocarcinomas (151.0), lupus erythematosus (710.0, 695.4), cystic fibrosis (277.0, 277.0X), hemochromatosis (275.0), acromegaly (253.0), Cushing's syndrome (255.0), Down syndrome (758.0), Klinefelter syndrome (758.7), Turner syndrome (758.6), Huntington chorea (333.4), or Laurence-Moon-Biedl syndrome (759.89).
- Patients using both CSII and CGM within one year of first diagnosis

Diabetes Type Algorithm

Previous studies have shown that T1DM diagnostic codes and insulin prescriptions can be used to identify pediatric T1DM patients in claims and EMR data with high specificity.[20,21,22,23] Using this information, we performed exploratory data analyses to develop an algorithm to differentiate between type 1 and type 2 diabetes in the MHS data. To achieve this, we created a cohort of patients with only type 1 (250.x1or 250.x3) or with only type 2 (250.x2) ICD-9 diagnostic codes. The characteristics of these

patients were used to differentiate between diabetes types for those patients where diagnostic codes were of mixed type or only included unspecified diabetes (250.00). The final differentiating algorithm was: at least two T1DM medication orders on separate days and (at least one T1DM diagnostic code or zero T2DM diagnostic codes).

Mode of Diabetic Treatment

Patients identified as T1DM were described by index treatment group. The index treatment was defined as the treatment method the patient was using on the index day (after completion of the 12 month baseline). Patients were described in the following three groups:

- MDI and SMBG (conventional therapy)
- MDI and CGM
- CSII and SMBG

For the purposes of this study, a treatment "switch" was defined as a change in insulin delivery method, from multiple daily injections to CSII. An "augment" was defined as initiation of CGM, as CGM is meant to be used in addition to SMBG. Once a patient initiated CSII and/or CGM, they were considered to be using the therapy until the end of follow-up. Patients using both CSII and CGM during the baseline period were excluded from the study, as they were not at risk of a switch or augment during follow-up.

Statistical Analyses

We calculated means and frequency distributions of patient characteristics to describe the study population as a whole and by treatment group at study entry. We

characterized patients at study entry in terms of age, gender, BMI at index, hemoglobin A1c at index, geographic region, and military branch and rank of sponsor and created Lowess plots of hemoglobin A1c centered on data of switch/augment to visualize changes in A1c occurring around the time of treatment change.

We created a linear multilevel mixed effects model to estimate the fixed effect of a treatment switch or augment on the subsequent hemoglobin A1c allowing for random intercepts within patients. Patient follow-up was divided into periods beginning and ending with a hemoglobin A1c measurement so that we could measure the difference in hemoglobin A1c between the start and end of a given period. Period duration, hemoglobin A1c before the treatment change, and significantly associated characteristics were adjusted for in the multivariate model. Indicator variables were created to indicate during which periods the patient chose to switch and/or augment treatment. Because hemoglobin A1c is the measure of average blood glucose over the past two to three months, we built in 30 day lag to allow some time for hemoglobin A1c to change after a switch/augment. Treatment indicators were also created to indicate during which periods patients used CSII and/or CGM, subsequent to a switch and/or augment. If, for example, a patient switched treatment during a given time period, for that period, the indicator for switch would equal one and the indicator for CSII would equal zero. For all subsequent time periods, the indicator for switch would revert to zero, but the indicator for CSII use would equal one. The mixed model was specifically designed to measure the difference between change in hemoglobin A1c in periods with a switch and/or augment and change in hemoglobin A1c in periods with no treatment change. Thus, we could measure the short-term effects of a treatment switch and/or augment. Using separate indicators for

switch/augment and continued CSII/CGM use allowed us to separately measure short-term as well as long-term changes in hemoglobin A1c in response to treatment.

We hypothesized there may be an interaction between a treatment switch and treatment augment, where patients changing from conventional therapy simultaneously to CSII and CGM may experience a benefit differing from the sum of each individual therapy. We also hypothesized that changes in hemoglobin A1c after initiation of CSII and/or CGM may depend on the hemoglobin A1c value preceding the treatment change so that patients with a higher initial A1c may experience greater reductions after a switch and/or augment. Interaction terms for these items were added to the model and tested for significance. We created three statistical models to estimate the effect of a treatment change on hemoglobin A1c: a minimal model which included only treatment indicators and hemoglobin A1c, a full model with all variables significantly associated in bivariate analyses, and a final reduced model created by including all significant covariates using backwards selection.

All statistical analyses were performed on the HRTx Citrix server using SAS version 9.3. Summaries from regression analyses of primary outcomes are displayed in the Tables. More complete statistical output is located in the Appendix.

Results

Patient Characteristics

Our study population consisted of 1,318 individuals, including 683 males and 635 females. The average age on the index day was 13.6 years old. The average first hemoglobin A1c recording was 9.1% (median: 8.7%) and the average first BMI

measurement was 23.9 kg/m^2. Multiple daily injections with self-monitoring of blood glucose (conventional therapy) was the most common (n=810; 61.5%) index therapy, followed by CSII with SMBG (n=502; 38.1%), and MDI with CGM (n=6; 0.5%). At study onset, a lower proportion of patients using CSII had a low military rank of sponsor (3.8% "Enlisted, Junior" vs. 6.0% for MDI) and higher proportion had a high sponsor rank (27.9% "Officer, Senior" vs. 13.0% for MDI) compared to patients using MDI ($p<0.0001$). Patient characteristics by index treatment group are displayed in Table 1. Patient selection and treatment patterns are displayed in Figure 1.

Crude Effects of Treatment Change on Hemoglobin A1c

Patients recorded 8,371 hemoglobin A1c measurements during follow-up, resulting in 7,053 time periods eligible for analysis. The mean period length was 170 days with a median of 120 days. There were 174 treatment switches and 159 augments, including 24 occurrences where a switch and augment occurred in the same time period. The average hemoglobin A1c during follow-up was 9.10% (median: 8.70%). The mean hemoglobin A1c before a treatment switch was 9.05% and the mean A1c before an augment was 8.78%. The average hemoglobin A1c preceding a period where a patient both switched and augmented therapy was 9.23%. On average, patients with no treatment change during a given period experienced a small (0.02%) increase in hemoglobin A1c; however, patients with a treatment switch (-0.53%), augment (-0.20%), or both (-0.77%) experienced a reduction. Lowess plots of hemoglobin A1c centered on switch (Figure 2) and augment (Figure 3) showed a visual reduction in A1c around the time of treatment change.

Mixed Models Measuring the Effects of Treatment Change on Hemoglobin A1c

The interaction between a treatment switch and augment was not statistically significant ($p=0.93$) and was not included in our final mixed model. However, terms for the interaction between the hemoglobin A1c measurement preceding a switch ($p<0.0001$) or an augment ($p=0.17$) were included in our multivariate models. In our final multivariate model, rank of sponsor ($p<0.0001$) and period duration ($p<0.0001$) were significantly associated with a change in hemoglobin A1c, but age ($p=0.61$), gender ($p=0.83$), military branch of sponsor ($p=0.74$), and geographic region ($p=0.50$) were not. We estimated that patients experienced a 0.57% ($p<0.0001$) average reduction in the next hemoglobin A1c for a switch and a 0.31% ($p=0.0016$) average reduction for an augment. For every 1% increase in hemoglobin A1c, patients experienced a 0.19% greater reduction in A1c from a switch and a 0.07% greater reduction from an augment. We predicted that patients with an initial hemoglobin A1c of 6% would experience no statistically significant changes in A1c after a treatment change. However, a patient with an initial A1c of 9% would experience a reduction of 0.55% from a switch and 0.30% from an augment, and a patient with a hemoglobin A1c of 12% would experience a reduction of 1.13% from a switch and 0.51% from an augment. Indicators for continued use of CSII ($p=0.16$) and CGM ($p=0.22$) were not statistically significant. Results from mixed effects models are displayed in Table 2 and estimated effects of a treatment change by initial hemoglobin A1c are displayed in Table 3.

Discussion

Summary of Main Findings

We found changes in hemoglobin A1c after a treatment change depended on the initial hemoglobin A1c. We estimated that patients with an initial A1c of 6% did not experience improved glycemic control from a treatment change, but for every 1% increase in initial hemoglobin A1c, patients experienced a 0.19% ($p<0.0001$) greater reduction in A1c from a switch and a 0.07% ($p=0.17$) greater reduction from an augment. There was no interaction ($p=0.93$) between a treatment switch and augment on the effect of hemoglobin A1c, suggesting the benefits of each treatment are additive in those patients who use both.

Effect of Treatment Change on Hemoglobin A1c

Early evidence, from the 1980's and1990's, of CSII demonstrated improvements in hemoglobin A1c compared to multiple daily injections.[24] However, with the development of improved short- and long-acting insulin analogs, the benefits in glycemic control of CSII over MDI have become less distinct. While some studies have shown no benefit from CSII,[25,26,27] others have shown modest improvements.[28,29] Meta analyses of clinical trials on the benefits of CSII on hemoglobin A1c have found reductions on the order 0.3% or less compared to MDI.[30,31,32] Furthermore, very few efficacy studies have focused on pediatric patients.[33]

In our study, we observed a reduction in hemoglobin A1c after initiation of CSII that was, on average, clinically meaningful (greater than 0.5%) among pediatric T1DM patients. It is important to note that our study was not designed to measure the treatment

effects of CSII as is done in clinical trials. Instead, we estimated the average change in hemoglobin A1c after initiation of CSII compared to patients without a treatment change. Our study observed greater reductions in hemoglobin A1c after initiation of CSII than has been demonstrated by randomized trials. The effects we observed would have been the sum of the average treatment effect and other influences, such as patient motivation.

A 2012 meta-analysis of clinical trials of CGM use in pediatric populations found an average improvement in hemoglobin A1c of approximately 0.3%.[34] Trials have not demonstrated reductions in severe hypoglycemic events,[35] though they have demonstrated reduced time spent in hypoglycemia (blood glucose < 70 mg/dL).[36] Our analyses estimated similar reductions in hemoglobin A1c after initiation of CGM as those estimated by clinical trials. We also observed, as have others,[37] that a higher hemoglobin A1c at baseline resulted in a greater reduction after a treatment change. Improvements in hemoglobin A1c after initiation of CGM were more modest compared to CSII. That continuous access to glucose levels does not result in greater improvements in glycemic control highlights the difficulty of maintaining glycemic homeostasis manually.

We hypothesized there may be an interaction between treatment switch and augment, where patients who chose both treatments may experience an extra benefit. However, our test of statistical interaction was not significant, suggesting the glycemic benefits of CSII and CGM use were additive. This means, on average, a patient in our cohort using conventional therapy with a hemoglobin A1c approximately 9%, would experience a 0.55% reduction from initiating CSII, a 0.30% reduction from initiating CGM, or a 0.85% reduction should they do both.

We hypothesized *a priori* that patients with higher initial hemoglobin A1c levels would experience a greater reduction in A1c after a change in treatment. We found this to be true; though, more so for a switch than for an augment. Even though the interaction between initial hemoglobin A1c and augment was not statistically significant, we decided to leave this interaction in the model for two reasons. First, we hypothesized *a priori* that this interaction was important. Second, the lack of significance is likely due to low power rather than the absence of any real effect. We estimated, for example, that patients with an initial hemoglobin A1c of 6%, would experience virtually no effects from a treatment change. However, patients with an initial hemoglobin A1c of 9% and 12% would experience average reductions in hemoglobin A1c that were clinically meaningful from a treatment switch or augment, respectively.

It is also of note that the average hemoglobin A1c was lower preceding an augment (8.78%) compared to measurements taken before a switch (9.05%). Evidence suggests improvements in glycemic control after initiation of CSII are likely sustained.[38,39] Because patients in our cohort predominately initiated CSII before CGM, it is intuitive that patients initiating CGM, many of whom have already experience an A1c reduction subsequent to initiating CSII, would on average have lower hemoglobin A1c levels compared to patients initiating CSII. Our study was not designed (or powered) to measure long-term trends in glycemic improvement. However, the indicators for continued CSII and CGM use after a treatment change were associated with very small changes in hemoglobin A1c and were not statistically significant. This suggests that the benefits of a treatment change are measurable by the next hemoglobin A1c reading and that there may be no increase, or attenuation, in benefit in the long run.

Strengths and Limitations

We hypothesized *a priori* that regression to the mean could occur among patients with high hemoglobin A1c levels. This would be of concern if high hemoglobin A1c was a motivating factor for a treatment change because regression to the mean could cause an artifact treatment effect. By using hemoglobin A1c at the end of each period as our dependent variable and adjusting for A1c levels at the beginning of the period, we estimated the difference in the predicted hemoglobin A1c after a treatment change compared to the predicted hemoglobin A1c when there was no treatment change while adjusting for the initial hemoglobin A1c (as well as other covariates). Thus, effects from regression to the mean were built into the predicted hemoglobin A1c. We chose to analyze our data using a mixed model so that we could account for regression to the mean as well as variable duration time periods, correlated data from repeated measures, and patient-level differences in hemoglobin A1c over time in our analyses.

This study was completed using EMR and insurance claims data, which has several strengths and limitations. Electronic data are readily available and are an efficient method for measuring outcomes for large cohorts of patients. Also, using claims data to describe treatment patterns of T1DM patients should capture nearly all insulin, CSII, and CGM related purchases as these treatments are expensive and unlikely to be paid for out of pocket.

There was likely some misclassification of diabetes type. Identification of patients with T1DM was based on algorithms developed during exploratory data analyses. It is possible, however, that some T1DM patients were missed and some T2DM patients were wrongfully included. Omission of T1DM patients may have reduced statistical power and

could have resulted in selection bias. Our differentiating algorithm was designed to be specific (rather than sensitive), so we believe it is unlikely that many patients with T2DM were wrongfully classified as type 1. This may reduce generalizability if patients who were omitted would have experienced different effects from a treatment change.

Another limitation of EMR/claims data is the lack of information on important confounders. For example, we were unable to adjust for sociodemographic indicators, including race and ethnicity, in our analyses because this information was missing for more than 99% of patients. However, evidence from the literature suggests that patient sociodemographics may not be a strong confounder for this analysis. By definition a confounder must be independently associated with an outcome and its exposure. Though race has been associated with higher hemoglobin A1c levels, (the outcome),[40] socioeconomic status may explain much of this effect.[41] Studies have also shown that socioeconomic characteristics, such as higher education and income, are superior predictors of CSII and CGM use (the exposure).[42,43,44] While we did not have household income or education data, we were able to use military rank of sponsor in our analysis, which we believed could be a socioeconomic indicator. We observed a strong relationship between increasing military rank of sponsor and increased likelihood of CSII/CGM use, which supports the hypothesis that sponsor rank may be a socioeconomic indicator.

Confounding by indication is also a well-established source of bias in these types of studies.[45] Patients who changed treatment were characteristically different than those who did not. Patients may differ in terms of demographics, overall health, economic security, access to healthcare, intelligence, motivation, and many other traits. Because

some of these characteristics cannot be measured and adjusted for in an observational study, treatment effects are not measured as they would be in a clinical trial setting. However, this was not a primary objective of this study. Where the purpose of a clinical trial is to measure effects attributable to the treatment, the purpose of this study was to measure the average effect experienced by patients who choose (or whose care givers choose) to change treatment after adjusting for important confounders. Thus, the effects we aimed to measured were the sum of the treatment effects from CSII/CGM and other factors associated with treatment choices that could not be measured.

Body mass index (BMI) was not included in the analysis because it was not available for every patient. We performed a sensitivity analysis to determine if most recently measured BMI would have made a meaningful difference in our estimates. BMI was not statistically significantly associated with hemoglobin A1c ($p=0.07$), and had virtually no effect on our estimates (see Table 4).

T1DM patients identified in this study may not be representative of the pediatric T1DM population in the United States. As the dependents of active and past military personnel, patients in this study are likely demographically different than the general US pediatric population and likely experience different levels of healthcare. However, removing our socioeconomic indicator, military rank of sponsor, had very little effect on any of our estimates. Therefore, we have no reason to believe that the treatment effects described in our study would vary greatly among different populations.

Conclusion

The purpose of this study was to estimate the benefits of a treatment change to continuous subcutaneous insulin infusion and/or continuous glucose monitoring on glycemic control in an observational cohort of pediatric patients with type 1 diabetes. We found that patients experienced a reduction in their next hemoglobin A1c after a change in treatment. This effect was greater among those patients with a higher initial hemoglobin A1c. Many patients in our cohort demonstrated clinically meaningful reductions in hemoglobin A1c after a treatment change.

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Tables

Table 1: Patient Characteristics by Initial Treatment (n=1,318).

Patient Characteristic	All Patients (N=1,318)	MDI and SMBG (N=810)	MDI and CGM (N=6)	CSII and SMBG (N=502)
Gender (n, %)				
Female	635 (48.2%)	376 (46.4%)	2 (33.3%)	257 (51.2%)
Male	683 (51.8%)	434 (53.6%)	4 (66.7%)	245 (48.8%)
Age [mean (SD)]	13.6 (3.6)	13.7 (3.7)	13.8 (4.4)	13.6 (3.4)
Body Mass Index [mean (SD)]	23.9 (5.0)	24.0 (5.3)	22.6 (2.9)	23.9 (4.6)
Hemoglobin A1c [mean (SD)]	9.1 (2.1)	9.3 (2.3)	9.4 (2.7)	8.8 (1.8)
Military branch (n, %)				
Army	498 (37.8%)	301 (37.2%)	3 (50.0%)	194 (38.6%)
Coast Guard	35 (2.7%)	26 (3.2%)	0 (0.0%)	9 (1.8%)
Air Force	368 (27.9%)	208 (25.7%)	2 (33.3%)	158 (31.5%)
Marine Corps	64 (4.9%)	39 (4.8%)	1 (16.7%)	24 (4.8%)
Navy	346 (26.3%)	233 (28.8%)	0 (0.0%)	113 (22.5%)
Other	7 (0.5%)	3 (0.4%)	0 (0.0%)	4 (0.8%)
Geographic region (n, %)				
West	215 (16.3%)	127 (15.7%)	0 (0.0%)	88 (17.5%)
Central	114 (8.6%)	67 (8.3%)	0 (0.0%)	47 (9.4%)
Northeast	542 (41.1%)	346 (42.7%)	2 (33.3%)	194 (38.6%)
Southeast	331 (25.1%)	183 (22.6%)	3 (50.0%)	145 (28.9%)
Alaska/Hawaii	65 (4.9%)	52 (6.4%)	0 (0.0%)	13 (2.6%)
Non-US	51 (3.9%)	35 (4.3%)	1 (16.7%)	15 (3.0%)
Rank of Sponsor (n, %)				
Enlisted, Junior	68 (5.2%)	49 (6.0%)	0 (0.0%)	19 (3.8%)
Enlisted, Senior	886 (67.2%)	590 (72.8%)	5 (83.3%)	291 (58.0%)
Warrant Officer	38 (2.9%)	19 (2.3%)	0 (0.0%)	19 (3.8%)
Officer, Junior	80 (6.1%)	47 (5.8%)	1 (16.7%)	32 (6.4%)
Officer, Senior	245 (18.6%)	105 (13.0%)	0 (0.0%)	140 (27.9%)
Other	1 (0.1%)	0 (0.0%)	0 (0.0%)	1 (0.2%)

Table 1 displays patient characteristics for all patients and by index treatment group. The index therapy refers to the mode of treatment being used on the first day after the 12-month baseline period.

Table2: Mixed Models for Changes in HbA1c After Treatment Change (n=1,318).

Effect	Model					
	Minimal*		Full**		Final***	
	Δ A1c % (95% C.L.)	p-value	Δ A1c % (95% C.L.)	p-value	Δ A1c % (95% C.L.)	p-value
Switch	-0.55 (-0.72, -0.37)	<0.0001	-0.56 (-0.75, -0.38)	<0.0001	-0.57 (-0.75, -0.39)	<.0001
Augment	-0.20 (-0.38, -0.01)	0.04	-0.30 (-0.50, -0.11)	0.002	-0.31 (-0.50, -0.12)	0.002
Switch*A1c Interaction	-0.19 (-0.28, -0.09)	<0.0001	-0.19 (-0.28, -0.10)	<0.0001	-0.19 (-0.28, -0.10)	<0.0001
Augment*A1c Interaction	-0.06 (-0.16, 0.04)	0.25	-0.07 (-0.17, 0.03)	0.17	-0.07 (-0.17, 0.03)	0.17
CSII	N/A		0.09 (-0.03, 0.21)	0.14	0.09 (-0.03, 0.20)	0.16
CGM	N/A		-0.08 (-0.21, 0.05)	0.25	-0.08 (-0.21, 0.04)	0.22

Table 2 displays the predicted change in hemoglobin A1c from initiation of CSII (switch) or CGM (augment) as well as the predicted effects of continued CSII and CGM use.

* Linear multilevel mixed effects model adjusted for initial hemoglobin A1c. Full results are displayed in Appendix Table 2.

** Linear multilevel mixed effects model adjusted for age, gender, military branch of sponsor, military rank of sponsor, geographic region, period length, and initial hemoglobin A1c. Full results are displayed in Appendix Table 3.

*** Linear multilevel mixed effects model adjusted for military rank of sponsor, period length, and initial hemoglobin A1c. Full results are displayed in Appendix Table 4.

Table 3: Expected Changes in Hemoglobin A1c After Treatment Change by Initial A1c Levels (n=1,318).

Effect	Hemoglobin A1c (%)	Model					
		Minimal*		Full**		Final***	
		Δ A1c % (95% C.L.)	p-value	Δ A1c % (95% C.L.)	p-value	Δ A1c % (95% C.L.)	p-value
Switch	6	0.03 (-0.31, 0.36)	0.88	0.03 (-0.31, 0.36)	0.87	0.02 (-0.31, 0.35)	0.91
	7	-0.16 (-0.42, 0.10)	0.22	-0.16 (-0.42, 0.10)	0.22	-0.17 (-0.43, 0.09)	0.20
	8	-0.35 (-0.54, -0.15)	0.0007	-0.35 (-0.56, -0.15)	0.0007	-0.36 (-0.57, -0.16)	0.0005
	9	-0.53 (-0.71, -0.35)	<0.0001	-0.54 (-0.73, -0.36)	<0.0001	-0.55 (-0.73, -0.37)	<0.0001
	10	-0.72 (-0.91, -0.52)	<0.0001	-0.73 (-0.94, -0.53)	<0.0001	-0.74 (-0.95, -0.54)	<0.0001
	11	-0.90 (-1.16, -0.65)	<0.0001	-0.93 (-1.18, -0.67)	<0.0001	-0.94 (-1.19, -0.68)	<0.0001
	12	-1.09 (-1.41, -0.76)	<0.0001	-1.12 (-1.45, -0.79)	<0.0001	-1.13 (-1.46, -0.80)	<0.0001
Augment	6	-0.02 (-0.35, 0.31)	0.91	-0.09 (-0.42, 0.24)	0.59	-0.10 (-0.42, 0.23)	0.57
	7	-0.08 (-0.33, 0.18)	0.55	-0.16 (-0.41, 0.10)	0.22	-0.16 (-0.42, 0.09)	0.21
	8	-0.13 (-0.33, 0.06)	0.19	-0.23 (-0.43, -0.02)	0.03	-0.23 (-0.43, -0.03)	0.02
	9	-0.19 (-0.38, -0.01)	0.04	-0.30 (-0.49, -0.11)	0.002	-0.30 (-0.49, -0.11)	0.002
	10	-0.25 (-0.47, -0.03)	0.03	-0.37 (-0.59, -0.14)	0.001	-0.37 (-0.59, -0.15)	0.001
	11	-0.31 (-0.59, -0.02)	0.04	-0.43 (-0.72, -0.15)	0.003	-0.44 (-0.73, -0.15)	0.003
	12	-0.36 (-0.73, 0.004)	0.05	-0.50 (-0.87, -0.14)	0.007	-0.51 (-0.87, -0.14)	0.007

Table 3 displays the predicted change in hemoglobin A1c from initiation of CSII (switch) or CGM (augment) by initial hemoglobin A1c from 6% to 12%.
* Linear multilevel mixed effects model adjusted for initial hemoglobin A1c. Detailed statistical results are displayed in Appendix Table 2.
** Linear multilevel mixed effects model adjusted for age, gender, military branch of sponsor, military rank of sponsor, geographic region, period length, and initial hemoglobin A1c. Detailed statistical results are displayed in Appendix Table 3.
*** Linear multilevel mixed effects model adjusted for military rank of sponsor, period length, and initial hemoglobin A1c. Detailed statistical results are displayed in Appendix Table 4.

Table 4: Mixed Model with BMI for Changes in HbA1c After Treatment Change.

Effect	Reduced Model without BMI*		Reduced Model with BMI**	
	Δ A1c % (95% C.L.)	**p-value**	**Δ A1c % (95% C.L.)**	**p-value**
Switch	-0.57 (-0.75, -0.39)	<.0001	-0.58 (-0.76, -0.40)	<.0001
Augment	-0.31 (-0.50, -0.12)	0.002	-0.31 (-0.50, -0.12)	0.002
Switch*A1c Interaction	-0.19 (-0.28, -0.10)	<0.0001	-0.19 (-0.28, -0.10)	<0.0001
Augment*A1c Interaction	-0.07 (-0.17, 0.03)	0.17	-0.07 (-0.17, 0.03)	0.16
CSII	0.09 (-0.03, 0.20)	0.16	0.08 (-0.04, 0.20)	0.20
CGM	-0.08 (-0.21, 0.04)	0.22	-0.08 (-0.21, 0.05)	0.21

Table 4 displays a comparison of the main analysis (n=1,318) and the sensitivity analysis (n=1,295) including patients with data for BMI.

* Linear multilevel mixed effects model adjusted for military rank of sponsor, period length, and initial hemoglobin A1c.

** Linear multilevel mixed effects model adjusted for BMI, military rank of sponsor, period length, and initial hemoglobin A1c.

Figures

Figure 1: Diagram of patient selection and treatment patterns.

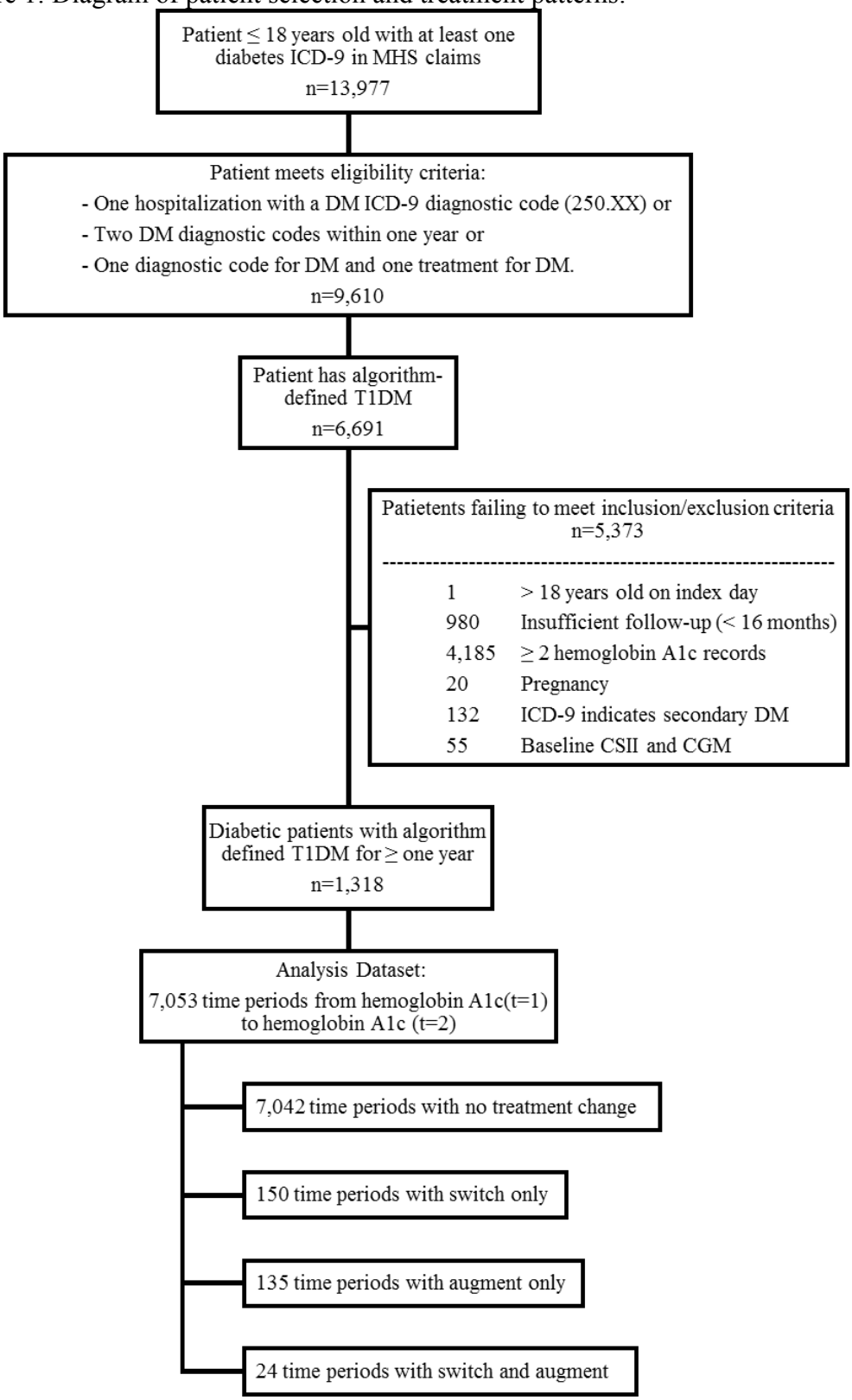

Figure 2: Lowess plot of hemoglobin A1c values centered around switch (n=174).

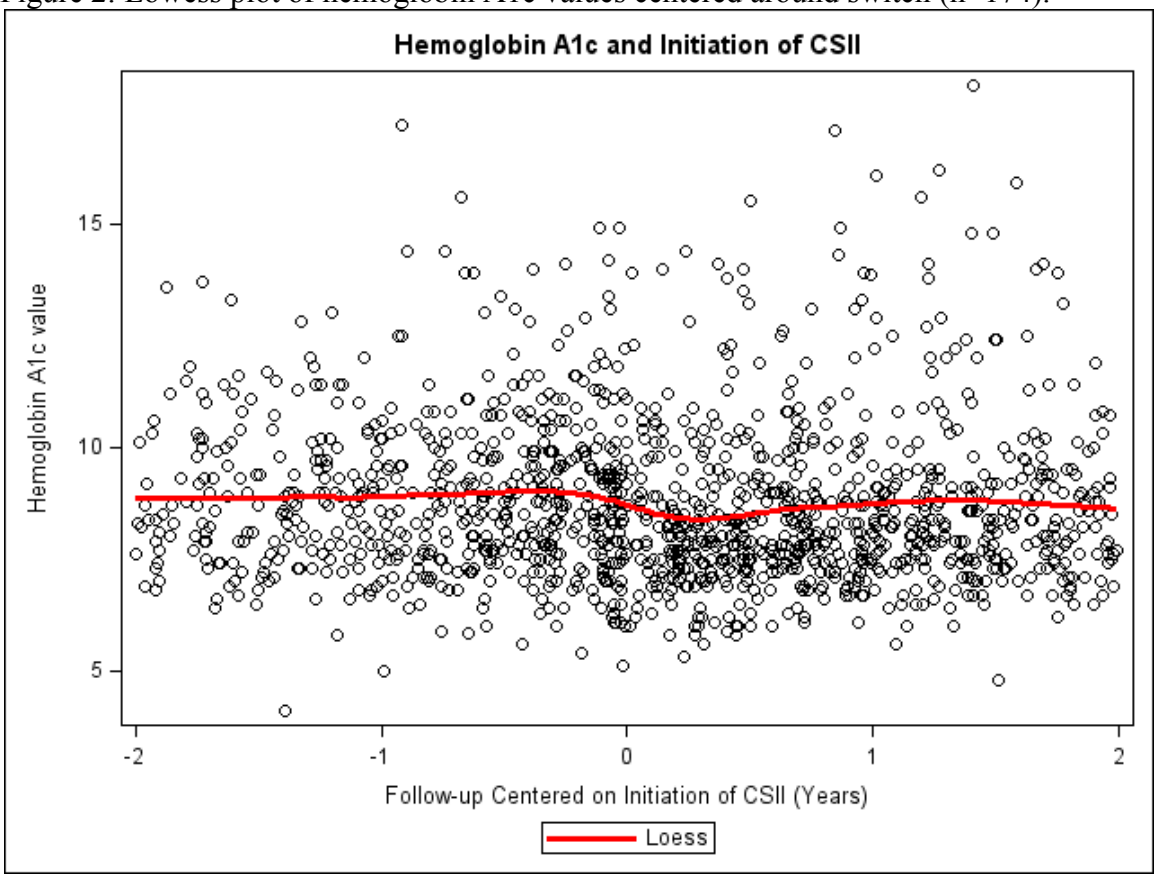

Figure 2 displays a Lowess plot of the average hemoglobin A1c during follow-up (years) among patients who initiated continuous subcutaneous insulin infusion (CSII) with follow-up time centered on the date of CSII initiation.

Figure 3: Lowess plot of hemoglobin A1c values centered around augment (n=149).

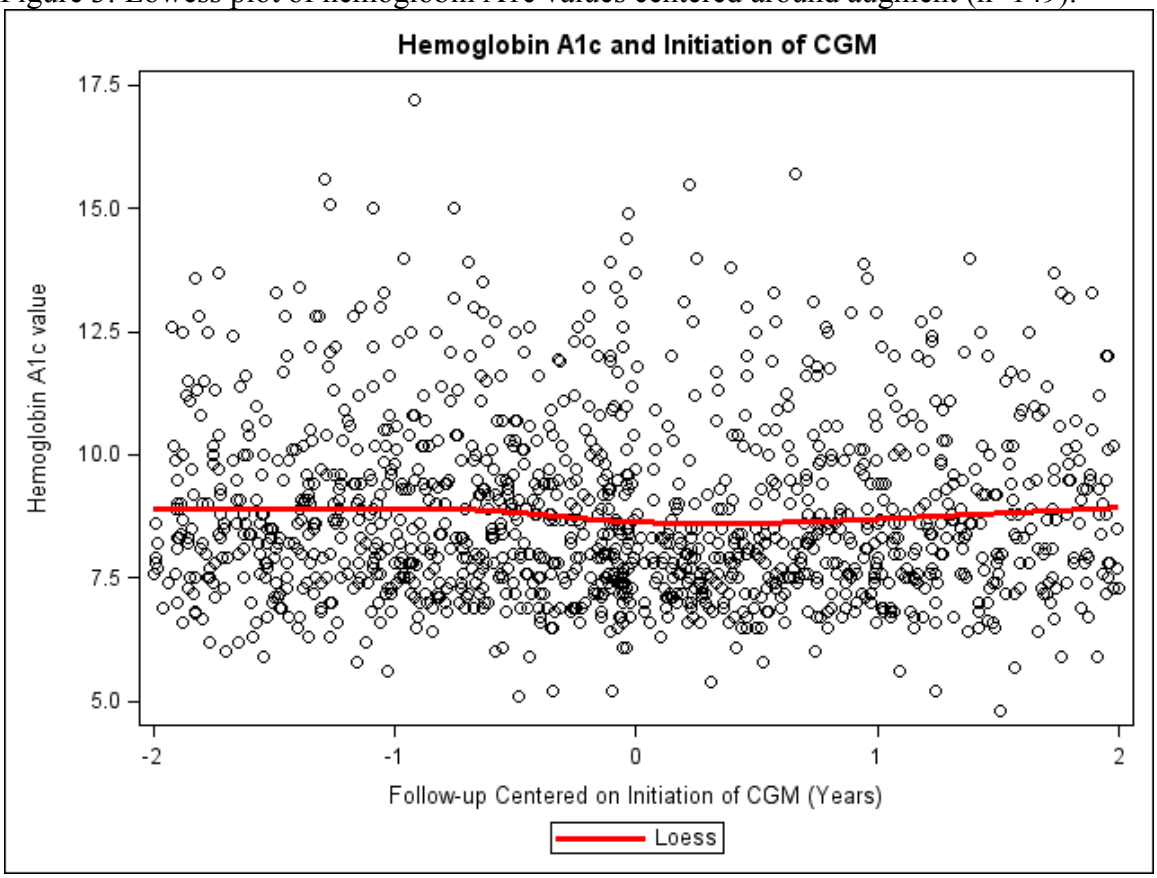

Figure 3 displays a Lowess plot of the average hemoglobin A1c during follow-up (years) among patients who initiated continuous glucose monitoring (CGM) with follow-up time centered on the date of CGM initiation.

Appendix Tables

Table A1: Patient Attrition.

Inclusion/Exclusion Criteria	Patients Remaining	Patients Excluded
Patient has a DM Dx	13,977 (100.0%)	
Patient has sufficient DM Dx/med criteria	9,610 (68.8%)	4,367 (31.2%)
Patient has algorithm defined T1DM	6,691 (47.9%)	2,919 (20.9%)
Patient was less than 18 years old at the time of first diagnosis	6,690 (47.9%)	1 (0.0%)
Patient has sufficient follow-up (16 months) enrollment	5,710 (40.9%)	980 (7.0%)
Patient has at least 2 eligible A1c records	1,525 (10.9%)	4,185 (29.9%)
Patient not excluded for pregnancy	1,505 (10.8%)	20 (0.1%)
Patient not excluded for condition Dx	1,373 (9.8%)	132 (0.9%)
Patient is at risk of switch or augment	1,318 (9.4%)	55 (0.4%)

Appendix Table 1 displays the number of patients excluded and the number of patient remaining after each inclusion/exclusion criteria. These data are also displayed in Figure 1.

Table A2: Minimal Mixed Model – Solution for Fixed Effects (n=1,318).

Effect	Level	Hemoglobin A1c %	Standard Error	t Value	Pr > |t|
Intercept		5.1832	0.5671	9.14	<.0001
Switch	No	-1.1356	0.4367	-2.6	0.0093
Switch	Yes	0	.	.	.
Augment	No	-0.3248	0.4475	-0.73	0.4679
Augment	Yes	0	.	.	.
Pre-A1c*Switch	No	0.5374	0.04981	10.79	<.0001
Pre-A1c*Switch	Yes	0.3523	0.06206	5.68	<.0001
Pre-A1c*Augment	No	0.05728	0.04994	1.15	0.2514
Pre-A1c*Augment	Yes	0	.	.	.
Pre-A1c Value		0	.	.	.

Differences of Least Squares Means

Effect	Δ A1c %	Standard Error	t Value	Pr > |t|	Lower C.L.	Upper C.L.
Switch	-0.5485	0.08969	-6.12	<.0001	-0.7244	-0.3727
Augment	-0.1963	0.09498	-2.07	0.0388	-0.3826	-0.01014

Appendix Table 2 displays statistical results from the minimal linear multilevel mixed effects model. The intercept for each patient was the sum of the fixed effect (shown above) and the patient-level random effect (not shown). Summary information from these data are also displayed in Table 2.

Table A3: Full Mixed Model – Solution for Fixed Effects (n=1,318).

Effect	Level	Hemoglobin A1c %	Standard Error	t Value	Pr > |t|
Intercept		4.6651	0.6548	7.12	<.0001
Switch	No	-1.1717	0.4351	-2.69	0.0071
Switch	Yes	0	.	.	.
Augment	No	-0.3236	0.4458	-0.73	0.468
Augment	Yes	0	.	.	.
Pre-A1c*Switch Int.	No	0.5106	0.04958	10.3	<.0001
Pre-A1c*Switch Int.	Yes	0.32	0.06176	5.18	<.0001
Pre-A1c*Augment Int.	No	0.06894	0.04968	1.39	0.1653
Pre-A1c*Augment Int.	Yes	0	.	.	.
CSII	No	-0.08977	0.06093	-1.47	0.1408
CSII	Yes	0	.	.	.
CGM	No	0.07599	0.06618	1.15	0.2509
CGM	Yes	0	.	.	.
Age		0.00304	0.00594	0.51	0.6091
Gender	Female	0.01022	0.04775	0.21	0.8306
Gender	Male	0	.	.	.
Sponsor	Air Force	0.3183	0.318	1	0.3169
Sponsor	Army	0.3707	0.3165	1.17	0.2416
Sponsor	Coast Guard	0.2672	0.3447	0.78	0.4383
Sponsor	Marine Corps	0.3621	0.3316	1.09	0.2749
Sponsor	Navy	0.3824	0.3164	1.21	0.2269
Sponsor	Other	0	.	.	.
Region	Alaska/Hawaii	-0.1923	0.1263	-1.52	0.1279
Region	Central	-0.06239	0.1091	-0.57	0.5673
Region	Non-US	0.00685	0.1393	0.05	0.9608
Region	Northeast	0.0325	0.06788	0.48	0.6321
Region	Southeast	0.01896	0.07961	0.24	0.8118
Region	West	0	.	.	.
Military Rank of Sponsor	Enlisted	0.2103	0.05343	3.94	<.0001
Military Rank of Sponsor	Officer	0	.	.	.
Period Length		0.00072	9.7E-05	7.39	<.0001
Pre-A1c Value		0	.	.	.

Differences of Least Squares Means

Effect	Δ A1c %	Standard Error	t Value	Pr > |t|	Lower C.L.	Upper C.L.
Switch	-0.563	0.09294	-6.06	<.0001	-0.7452	-0.3808
Augment	-0.3036	0.09781	-3.1	0.0019	-0.4954	-0.1119
CSII	0.08977	0.06093	1.47	0.1408	-0.02969	0.2092
CGM	-0.076	0.06618	-1.15	0.2509	-0.2057	0.05374

Appendix Table 3 displays statistical results from the full linear multilevel mixed effects model. The intercept for each patient was the sum of the fixed effect (shown above) and the patient-level random effect (not shown). Summary information from these data are also displayed in Table 2.

Table A4: Reduced Mixed Model – Solution for Fixed Effects (n=1,318).

Effect	Level	Hemoglobin A1c %	Standard Error	t Value	Pr > |t|
Intercept		4.9936	0.5743	8.69	<.0001
Switch	No	-1.1671	0.4353	-2.68	0.0074
Switch	Yes	0	.	.	.
Augment	No	-0.3164	0.4457	-0.71	0.4779
Augment	Yes	0	.	.	.
Pre-A1c*Switch Int.	No	0.5181	0.04957	10.45	<.0001
Pre-A1c*Switch Int.	Yes	0.327	0.06176	5.29	<.0001
Pre-A1c*Augment Int.	No	0.06858	0.04968	1.38	0.1675
Pre-A1c*Augment Int.	Yes	0	.	.	.
CSII	No	-0.0857	0.06038	-1.42	0.1558
CSII	Yes	0	.	.	.
CGM	No	0.07996	0.06493	1.23	0.2182
CGM	Yes	0	.	.	.
Military Rank of Sponsor	Enlisted	0.2142	0.05213	4.11	<.0001
Military Rank of Sponsor	Officer	0	.	.	.
Period Length		0.000708	0.000095	7.45	<.0001
Pre-A1c Value		0	.	.	.

Differences of Least Squares Means

Effect	A1c	Δ A1c %	Standard Error	t Value	Pr > |t|	Lower C.L.	Upper C.L.
Switch	9.1	-0.5723	0.0926	-6.18	<.0001	-0.7538	-0.3907
Augment	9.1	-0.3076	0.09763	-3.15	0.0016	-0.499	-0.1162
CSII	9.1	0.0857	0.06038	1.42	0.1558	-0.03266	0.2041
CGM	9.1	-0.08	0.06493	-1.23	0.2182	-0.2072	0.04732
Switch	6	0.0201	0.1697	0.12	0.9057	-0.3126	0.3528
Switch	7	-0.1711	0.1327	-1.29	0.1974	-0.4312	0.08905
Switch	8	-0.3622	0.1042	-3.48	0.0005	-0.5665	-0.158
Switch	9	-0.5534	0.09252	-5.98	<.0001	-0.7348	-0.372
Switch	10	-0.7445	0.1035	-7.19	<.0001	-0.9474	-0.5416
Switch	11	-0.9357	0.1316	-7.11	<.0001	-1.1937	-0.6777
Switch	12	-1.1269	0.1684	-6.69	<.0001	-1.4571	-0.7967
Augment	6	-0.0951	0.1675	-0.57	0.5702	-0.4235	0.2333
Augment	7	-0.1637	0.13	-1.26	0.208	-0.4185	0.09114
Augment	8	-0.2323	0.1033	-2.25	0.0246	-0.4348	-0.02972
Augment	9	-0.3008	0.0969	-3.1	0.0019	-0.4908	-0.1109
Augment	10	-0.3694	0.1142	-3.23	0.0012	-0.5933	-0.1455
Augment	11	-0.438	0.1471	-2.98	0.0029	-0.7263	-0.1497
Augment	12	-0.5066	0.1875	-2.7	0.0069	-0.8741	-0.139

Appendix Table 4 displays statistical results from the final reduced linear multilevel mixed effects model. The intercept for each patient was the sum of the fixed effect (shown above) and the patient-level random effect (not shown). Summary information from these data are also displayed in Tables 2, 3 and 4.

CHAPTER 4: MANUSCRIPT 3 – EMERGENCY CARE

Abstract

Purpose: The purpose of this study was to estimate the effects of continuous subcutaneous insulin infusion (CSII) and/or continuous glucose monitoring (CGM) on emergency care utilization in an observational cohort of pediatric patients with type 1 diabetes mellitus (T1DM).

Methods: This study was performed using data extracted from the US Department of Defense (DOD) Military Health Systems (MHS) database between October 2007 and September 2013. Exploratory analyses were performed to develop an algorithm designed to identify diabetic patients and differentiate between type 1 and type 2 diabetes. We created a zero-inflated Poisson model to estimate the effects of switching insulin delivery method from multiple daily injections (MDI) to CSII and/or augmenting treatment with a CGM on emergency care utilization.

Results: Our study population consisted of 3,138 pediatric patients with T1DM using conventional therapy (multiple daily injections and self-monitoring of blood glucose). During follow-up, 62.6% (n=1,964) of patients remained on conventional therapy and 37.4% (n=1,174) of patients changed treatment. We observed 21,371 total emergency care days during 9,940 patient years of follow-up (2.15 total emergency care days per patient year). We observed that patients initiating CSII (RR = 0.81; $p<0.0001$) and CGM (RR = 0.88; $p<0.0059$) experienced a decrease in total emergency care days. Patients using both CSII and CGM (RR = 0.85) did not experience added benefit from multiple treatments.

Conclusion: We found that patients who changed treatment from conventional therapy to CSII and/or CGM experienced a statistically significant reduction in the number of days with emergency care.

Introduction

Type 1 diabetes mellitus (T1DM) is an autoimmune disease where the insulin producing (beta) cells in the pancreas are destroyed. Consequently, T1DM patients lose endogenous glycemic control and must attempt to maintain euglycemia manually through insulin injection and blood glucose monitoring. Consequences of dysglycemia include diabetic ketoacidosis (DKA) and severe hypoglycemia (SH). These acute complications of type 1 diabetes frequently result in emergency care[1,2] and are responsible for nearly 80% of deaths in the first decade after diagnosis.[3]

Insufficient insulin and infection are the most common causes of diabetic ketoacidosis.[4,5,6] While patients with high hemoglobin A1c levels are at greater risk for DKA,[7] severe hypoglycemia is associated with a lower A1c,[8] as well as high glucose variability.[9] SH is also more common among patients with longer duration of diabetes because these patients are more likely to exhibit hypoglycemic unawareness.[10]

Type 1 diabetic patients inject insulin either through multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII), also known as an insulin pump. T1DM patients must also monitor blood glucose levels to inform insulin dosing decisions. Glucose monitoring is traditionally done through self-monitoring of blood glucose (SMBG), where the patient must prick their finger multiple times daily to take a blood glucose reading. Some patients also choose to use a continuous glucose monitor (CGM), a device attached to the patient that estimates blood glucose levels by continuously reading glucose levels in interstitial fluid using a wire sensor inserted under the skin.

Fewer than one in four US children with T1DM have a hemoglobin A1c less than the American Diabetes Association (ADA) recommended value of 7.5%.[11] Poor glycemic

control is largely due to fear of hypoglycemia.[12,13,14] Patients' treatment choices play an important role in glycemic control as well as the risk of acute complications of diabetes. Conventional insulin therapy (CIT) is a treatment regimen characterized as having few injections with meals scheduled around peaks in insulin activity. CIT is designed around structure, where insulin dosages, meal timing, and carbohydrate load are consistent from day to day. Flexible intensive insulin therapy (FIIT) is a newer insulin regimen characterized by flexible meal times with frequent injections designed to more appropriately adhere to a typical lifestyle. FIIT has been shown to improve hemoglobin A1c and reduce the risk of SH and DKA compared to CIT.[15,16]

As CSII became a more popular treatment, many physicians were concerned infusion site failures would increase risk of DKA. When infusion of rapid-acting insulin stops, insulinopenia develops quickly[17] and may progress to DKA. However, studies suggest there may be decreased risk of ketoacidosis among patients using CSII as well as a decreased risk of severe hypoglycemia. [18,19,20]

Increased frequency of SMBG has been shown to lower hemoglobin A1c without increased risk of SH.[21] CGM use has been shown to reduce time spent in hypoglycemia. [22] However, evidence of the effectiveness of CGM use at reducing risk of acute complications of T1DM is mixed with some studies suggesting a reduction in SH and/or DKA[23,24,25] and some finding no association.[26,27]

We hypothesized that if CSII and/or CGM reduce the risk of acute complications among T1DM patients, it should translate into fewer days spent in emergency care. To test this hypothesis, we created a cohort of pediatric patients with type 1 diabetes using insurance claims data. All patients had T1DM for at least one year and were using MDI

and SMBG at baseline. The purpose of our study was to estimate changes in the number of emergency care days subsequent to initiation of CSII and/or CGM.

Methods

Study Population

This study was performed using data extracted from the US Department of Defense (DOD) Military Health Systems (MHS) database. The DOD MHS serves active and past military personnel (known as the sponsor) and their dependents. The database includes both an electronic medical record (EMR) and a medical insurance claims component. All patients are included in the insurance claims data, and approximately one third have EMR data. Data collected includes: demographics, diagnostic codes, information on medical procedures, symptoms, vital signs, laboratory and radiology results, and pharmacy orders and claims. The crude data, prepared by Health Research Tx (HRTx), included all EMR encounters and insurance claims for patients with at least one International Classification of Diseases, Ninth Revision (ICD-9) diagnostic code indicating diabetes (250.XX) before their 19th birthday. All personal identifiable information was removed. At the time of extraction, data were available between October 2007 and September 2013.

Patients in the DOD MHS dataset during the study period meeting the following criteria were selected for this study:

- At least one of the following:
    - One hospitalization with an ICD-9 diagnostic code for DM (250.XX)
    - Two DM diagnostic codes within one year
    - One diagnostic code for DM and one treatment for DM

- Patient has algorithm defined type 1 diabetes
- Age 18 years or younger at first diabetes diagnosis
- A minimum of 18 months of enrollment after first DM diagnosis

Previous studies, [28,29] as well as our own exploratory analyses, have shown that glycemic control varies drastically during the first year after type 1 diabetes diagnosis. Because we could not perfectly distinguish between incident and prevalent diabetes, we required a 12 month baseline period after the first indication of T1DM in the data, and no outcomes were measured until completion of the baseline period. Among patients meeting the eligibility criteria, the first day after the completion of the baseline period was considered the index day for the study. We also required a minimum of 6 months of follow-up. These requirements enabled us to create cohort with established, and more stable, diabetes and with enough follow-up to observe emergency care utilization.

Exclusion criteria were chosen to reduce the number of patients with gestational or other secondary (non-type 1 or 2) diabetes. Patients also needed to be using conventional therapy on the index day so they would be at risk of a treatment change. Patients meeting the following criteria were excluded from the study:

- Patients becoming pregnant less than six months after index date were excluded. (Patients becoming pregnant greater than six months after index were censored at the pregnancy date.)
- Patients with an ICD-9 code indicating any of the following: secondary diabetes (249.x), other endocrine dysfunction (251.8), adrenal cortical steroids causing adverse effects in therapeutic use (E932.0), adenocarcinomas (151.0), lupus erythematosus (710.0, 695.4), cystic fibrosis (277.0, 277.0X), hemochromatosis (275.0), acromegaly (253.0), Cushing's syndrome (255.0), Down syndrome

(758.0), Klinefelter syndrome (758.7), Turner syndrome (758.6), Huntington chorea (333.4), or Laurence-Moon-Biedl syndrome (759.89).

- Patients using CSII or CGM within one year of first diagnosis

Diabetes Type Algorithm

Previous studies have shown T1DM diagnostic codes and insulin prescriptions can be used to identify pediatric T1DM patients in claims and EMR data with high specificity.[30,31,32,33] Using this information, we performed exploratory data analyses to develop an algorithm to differentiate between type 1 and type 2 diabetes in the MHS data. To achieve this, we created a cohort of patients with only type 1 (250.x1or 250.x3) or with only type 2 (250.x2) ICD-9 diagnostic codes. The characteristics of these patients were used to differentiate between diabetes types for those patients where diagnostic codes were of mixed type or only included unspecified diabetes (250.00). The final differentiating algorithm was: at least two T1DM medication orders on separate days and (at least one T1DM diagnostic code or zero T2DM diagnostic codes).

Mode of Diabetic Treatment

All patients were using conventional therapy (MDI and SMBG) on the index day. Patients using CSII or CGM on or before the end of the baseline period were excluded so that only patients at risk of both treatment changes remained. For the purposes of this study, a treatment "switch" was defined as a change in insulin delivery method from multiple daily injections to CSII. An "augment" was defined as initiation of CGM as CGM is meant to be used in addition to SMBG. Once a patient initiated CSII and/or CGM, they were considered to be using the therapy until the end of follow-up.

Measures of Acute Dysglycemia

We used emergency care days as a measure of acute complications of dysglycemia. Patients with severe hypoglycemia frequently require ambulance or emergency room services,[34] and those with DKA are often hospitalized.[35,36] Therefore, we counted all hospitalization days, emergency room/ambulance days, and total emergency (hospitalization and/or ER/ambulance) care days during follow-up. These counts were the primary outcomes for our analyses.

By counting hospitalizations and ER/ambulance days separately, we attempted to estimate the effect of CSII and CGM on ketoacidosis and severe hypoglycemia separately and in total. Total emergency care days was our measure for all acute complications. We performed exploratory data analyses to test these assumptions by calculating proportion of emergency encounters with any SH (250.12) and DKA (250.1x) ICD-9 diagnostics codes (see "*Effects of Treatment on Acute Complications of T1DM*" in the Discussion).

Statistical Analyses

We created means and frequency distributions of patient characteristics to describe the study population at study entry. We characterized patients in terms of age, gender, BMI on index day, hemoglobin A1c on index day, geographic region, and military branch and rank of sponsor.

The primary outcome of our study was the number of days with emergency care in each 6-month time segment. We used zero-inflated Poisson regression to estimate the effects of a treatment change on utilization of emergency care. Patient follow-up was divided into 6-month periods to allow time for emergency care encounters, and indicator variables were created to indicate treatment during each period. Hospitalization days,

emergency room/ambulance days, and total emergency (hospitalization and/or ER/ambulance) care days were counted during each period. Bivariate, full, and final backwards selection models were created to estimate the changes in the number of each type of emergency care day (hospital, ER/ambulance, and total) after a switch and/or augment. We hypothesized there may be interaction between CSII and CGM use, where patients using both may experience a benefit that differs from the sum of each individual treatment. Consequently, an interaction term was added to the model and tested for significance. Estimates for the effects of CSII and CGM on utilization of emergency care were calculated in the form of rate ratios (RRs).

We also performed a secondary analysis to assess the association between CSII and CGM use and utilization of diabetes-related emergency care. In this analysis, only emergency care with a diabetes-related (250.XX) primary diagnosis was counted. All other aspects of the model were consistent with the primary analysis.

All statistical analyses were performed on the HRTx Citrix server using SAS version 9.3. Summaries from regression analyses of primary outcomes are displayed in the Tables. More complete statistical output is located in the Appendix.

Results

Patient Characteristics

Our study population consisted of 3,138 individuals including 1,769 males and 1,369 females. The average age at study entry (after baseline) was 13.8 years old. Among patients with EMR data, the average first hemoglobin A1c recording was 9.3% (median: 9.0%) and the average first BMI measurement was 23.6 kg/m^2 (median: 23.0 kg/m^2). All

patients were using conventional therapy at study entry. Patient characteristics are displayed in Table 1. Patient selection and treatment patterns are displayed in Figure 1.

Treatment Patterns

During follow-up, 62.6% (n=1,964) of patients remained on conventional therapy, while 37.4% (n=1,174) of patients changed treatment. Nearly 90% (n=1,056) of patients changing treatment initiated CSII, including 31.9% (n=375) who initiated CSII and CGM. Only 3.8% (n=118) of the patients in the cohort augmented with CGM without also switching to CSII. Treatment patterns are displayed in Table 2.

Emergency Care Utilization

The average duration of patient follow-up was 3.2 years, giving a total of 9,940 patient years for analysis. During this time, we observed 21,371 total emergency care days, including 13,986 hospitalization days and 12,858 ER/ambulance days, which translates to 1.29 ER/ambulance days, 1.41 hospital days, and 2.15 total emergency care days per patient year. On average, in a 6-month period, 28% of patients utilized emergency care including 27% with at least one ER or ambulance encounter and 9% with a hospitalization. The distributions of average emergency care utilization per 6-month period for total emergency care, ER/ambulance care, and hospitalizations are displayed in Figures 2, 3, and 4, respectively. DKA was the most common diagnosis for all types of emergency care, followed by other ICD-9 codes related to type 1 diabetes. DKA diagnostic codes were present in approximately 44% of hospital records, 19% of ER records, and 8% of ambulance claims. Hypoglycemia codes were very rare in the data,

present in fewer than 2% of ER records, less than 1% of ambulance records, and virtually absent in hospitalization records.

Zero inflated Poisson models consist of two parts, a model for predicting excess zeros and a Poisson model. In our final regression model, gender, age, military rank of sponsor, and geographic region were associated with zero counts. Female gender (RR=1.13; $p<0.0001$), older age (RR=1.05; $p<0.0001$), "Enlisted" military rank of sponsor (RR=1.12; $p<0.0001$), and living in the western US ($p<0.0001$) were all associated with increased risk for emergency care utilization. We estimated CSII usage decreased hospitalization days (RR=0.75; $p<0.0001$), ER/ambulance days (RR=0.94; $p=0.02$), and total emergency care days (RR=0.81; $p<0.0001$). Similarly, patients using a CGM demonstrated fewer hospitalization days (RR=0.89; $p=0.03$), ER/ambulance days (RR=0.85; $p=0.02$), and total emergency care days (RR=0.88; $p=0.006$). The interaction between CSII and CGM was statistically significant in each model, showing reduced effectiveness from multiple treatments. Patients using both CSII and CGM spent fewer days in the hospital (RR=0.80; $p<0.0001$) and had fewer total emergency care days (RR=0.85; $p<0.0001$) compared to patients who remained on conventional therapy; however, there was no difference in the number of days with an ER/ambulance encounter (RR=1.04; $p=0.32$). Results of the effects of treatment on each type of emergency care are displayed in Tables 3 through 5.

Initiation of CSII, CGM, or both had statistically similar results on the effects of total emergency care utilization. The effects of initiating CSII and the effects of initiating CGM were not statistically different ($p=0.10$). Further, initiating CGM after CSII (0.21) or CSII after CGM (0.51) added no benefit in the reduction of emergency care. A

comparison of effects from each treatment combination on total emergency care is displayed in Table 6.

In our secondary analysis, we estimated CSII use was associated with reduced utilization of total emergency care (RR=0.90; p<0.0001) and hospitalization days (RR=0.87; p<0.0001); however, CSII was not associated (RR=1.01; p=0.86) with the number of days with an ER/ambulance encounter. Patients using a CGM demonstrated fewer hospitalization days (RR=0.81; p=0.002), ER/ambulance days (RR=0.88; p=0.008), and total emergency care days (RR=0.90; p=0.003). The interaction between CSII and CGM was statistically significant for hospitalization days but not for ER/ambulance days and total emergency care days. Patients using both CSII and CGM experienced fewer days in the hospital (R =0.84; p=0.0001) compared to patients who remained on conventional therapy. Results from the secondary analysis are displayed in Tables 7 through 9.

Discussion

Summary of Main Findings

Our study suggests patients who initiate continuous subcutaneous insulin infusion and/or continuous glucose monitoring experience a significant reduction in the utilization of emergency care. More than one third of the patients in the cohort changed treatment during follow-up. We observed 2.15 total emergency care days per patient year and estimated that switching treatment to CSII reduced days utilizing emergency care by 19%, augmenting with a CGM resulted in a 12% reduction in emergency care days, and initiating both CSII and CGM reduced days with emergency care by 15%. CSII was associated with a larger reduction in total hospital days, while CGM use was associated

with a larger reduction in ER/ambulance care days. All treatment combinations including CSII and/or CGM had statistically similar effects.

Treatment Changes and Acute Complications of T1DM

We hypothesized ambulance and emergency room encounters were more likely to capture episodes of severe hypoglycemia, while hospitalizations would be more likely to measure ketoacidosis encounters. While this was true, DKA was the most commonly recorded diagnostic code for all types of encounters. Furthermore, as prevalent as DKA codes were, SH codes were quite rare. This suggests either most episodes of SH occur outside of an emergency care setting or SH was poorly recorded in our data (or both).

Because DKA and SH did not separately correlate well with hospitalization days and ER/ambulance days, we are unable to estimate whether patients initiating CSII and/or CGM therapy experience reductions in DKA and SH, specifically. However, because we observed significant reductions in the number of days with ER/ambulance, hospitalization, and total emergency care, we can infer that patients initiating CSII and/or CGM do experience a reduction in emergency care utilization.

Emergency Care Days

Other studies have reported incidence rates of acute complications of T1DM. A 2008 meta-analysis of clinical trial data estimated the incidence of severe hypoglycemia was 36 events per 100 patient years for children and 100 events per 100 patient years for adults.[37] US studies have estimated the rate of DKA among type 1 diabetics to be 8 to 10 events per 100 patient years;[38,39] however, hospital admission rates among adolescence with poor metabolic control is likely several times higher.[40] International studies

describing incidence of DKA among type 1 diabetics have reported between 5 and 26 events per 100 patient years.[41,42,43]

It is an important distinction that we were not directly measuring severe hypoglycemia and diabetic ketoacidosis encounters. Instead, we measured emergency care days. Moreover, we believed diabetes is sometimes an indirect cause of emergency care. Therefore, in our primary analysis we included all emergency care days in our analyses instead of limiting to diabetes related emergency care days. It is also important to note the difference between measuring the incidence of events, as discussed above, and measuring care days, as we did. A Canadian study found average length of diabetes related hospital stay is 3.5 days for non-DKA admissions and 3.2 days for DKA-related admissions.[44] Our study was designed to detect differences in emergency care days as a result of treatment, which may have been a result of fewer and/or shorter emergency care events. However, we were unable to determine if patients in our study experienced a reduction in the number of events or fewer days per event (or both).

The interaction between CSII and CGM showed no added benefit from a second treatment. Any combination of treatments including CSII and/or CGM showed a statistically significant reduction in the utilization of total emergency care; however, they were statistically equivalent to each other. There are several possible explanations for this. The most likely explanation is that this effect was due to confounding by indication. Patients initiating both CSII and CGM during the study period may have been less healthy than their comparators. Consequently, they may have been more likely to utilize emergency care. It is also possible that after initiating CSII or CGM patients reach their highest achievable level of control so that adding a second therapy is not beneficial.

Our secondary analysis restricted emergency care days to encounters with diabetes-related diagnostic codes. Interestingly, we found CSII therapy had a larger effect on overall emergency care (RR=0.81) than on emergency care directly related to diabetes (RR=0.90). The effect of CSII was smaller on diabetes-related hospitalizations (RR=0.87) than total hospitalizations (RR=0.75), and there was no association between CSII use and diabetes-related ER/ambulance days (RR=1.01). CGM use had a greater effect on diabetes-related hospitalization days (RR=0.81) than in total hospitalization days (RR=0.89) while the effect on other diabetes-related and total emergency care days were similar. These results suggest that CSII and CGM may have a significant impact on reducing the need for emergency care in situations where diabetes is secondary to another ailment. Though, it is also possible that some emergency care encounters related to diabetes were not appropriately coded.

Gender

Previous studies have reported female T1DM patients have higher healthcare costs[45] and are at higher risk of severe hypoglycemia and diabetic ketoacidosis compared to male T1DM patients.[46,47] The results of our study were consistent with this observation. We estimated female gender was associated with 10% more ER/ambulance days, 7% more hospitalization days, and 13% more total emergency care days compared to males.

Sensitivity Analyses

We performed several sensitivity analyses to test the robustness of our results. First, we tried using alternative statistical models to see if we would get different results.

Estimates from multilevel models assuming a Poisson or binomial distribution were similar in magnitude and showed the same patterns to those from the zero-inflated Poisson model: CSII had a slightly larger effect compared to CGM for total emergency care and hospitalizations and CGM had a larger effect on ER/ambulance care. However, in both multilevel models, standard errors were larger than in our zero-inflated models resulting in wider confidence intervals and reduced statistical significance. Exploratory analyses showed our outcomes were clearly zero-inflated (see Figures 2 through 4), so we decided zero-inflated Poisson was the best model for our data.

We also ran a zero-inflated Poisson model where patients did not have to be using conventional therapy at study entry. Patients using CSII or CGM (but not both) at study entry were included in this analysis. To account for index therapy, we created indictor variables for treatment at study entry. Again, our estimates were very similar to those in the main analysis model, only with slightly larger standard errors and inferior model fit (higher AIC).

Considerations

Due to the zero-inflated nature of our data, we decided zero-inflated Poisson regression was the best statistical model to analyze counts of emergency care days. We ran sensitivity analyses (described above) to determine how the statistical model we chose affected our results and observed that estimates between models were similar. The main shortfall of zero-inflated regression is it does not account for correlated data. By not accounting for correlations from repeated measures within subjects, standard errors are underestimated. Consequently, by using zero-inflated regression, we slightly overestimated the precision and statistical significance of our estimates.

Because patients could experience more than one change in treatment, we could not center time periods on a treatment change. Therefore, time periods began on the index day, and treatment changes occurred at some point during a given period. This means all emergency care days experienced in a period included a change in treatment were analyzed as if they occurred after the treatment change even if they occurred beforehand. This could have biased our estimates towards no association if emergency care encounters motivate patients to initiate CSII or CGM shortly thereafter. We performed a sensitivity analysis to see how our estimates would be different if treatment changes occurring after the midpoint of a period were not counted until the next period. We found this had little effect on our estimates (see Table 10).

We only included T1DM patients with at least one year of diabetes in our analyses. Therefore, we were unable to measure the effects of CSII and CGM among patients who chose these treatments quickly after diagnosis. It is possible early adapters could have experienced different treatment effects than those observed in our study.

This study was completed using EMR and insurance claims data, which has several strengths and limitations. Electronic data are readily available, and a cost and time efficient way to measure outcomes for large cohorts of patients. Also, using claims data to describe treatment patterns of T1DM patients should capture nearly all insulin, CSII, and CGM related purchases as these treatments are expensive and unlikely to be paid for out of pocket.

There was likely some misclassification of diabetes type. Identification of patients with T1DM was based on algorithms developed during exploratory data analyses. It is possible, however, that some T1DM patients were missed and some T2DM patients were wrongfully included. Omission of T1DM patients may have reduced statistical power and

could possibly have resulted in selection bias. Our differentiating algorithm was designed to be specific (rather than sensitive), so we believe it is unlikely that many patients with T2DM were wrongfully classified as type 1.

Another limitation of EMR/claims data is the lack of information on important confounders. For example, we were unable to adjust for sociodemographic indicators, including race and ethnicity, in our analyses because this information was missing for more than 99% of patients. However, evidence from the literature suggests patient sociodemographics may not be a strong confounder for this analysis. By definition, a confounder must be independently associated with an outcome and its exposure. Though race has been correlated with increased risk of acute complications of type 1 diabetes (the outcome),[48] so has lower socioeconomic status.[49] Studies have also shown socioeconomic characteristics, such as higher education and income, are superior predictors of CSII and CGM use (the exposure).[50,51,52] While we did not have household income or education data, we were able to use military rank of sponsor in our analysis, which we believed could be a socioeconomic indicator. We observed a strong relationship between increasing military rank of sponsor and increased likelihood of CSII/CGM use, which supports the hypothesis that sponsor rank may be a socioeconomic indicator.

Body mass index (BMI) and hemoglobin A1c were not included in the analysis because they were not available for every patient. Only 48% of our patients had at least one BMI measurement during follow-up, and only 34% of patients had a hemoglobin A1c measurement. We performed a *post hoc* analysis to determine if BMI and hemoglobin A1c would have made a meaningful difference in our estimates. Both BMI ($p=0.0024$) and hemoglobin A1c ($p<0.0001$) were statistically significantly associated with total emergency care days. In models where BMI and hemoglobin A1c were

included, estimates of reductions in emergency care utilization after initiation of CSII and/or CGM were increased. However, we decided not to include BMI and hemoglobin A1c in our final models for three reasons. First, and most importantly, our analysis plan *a priori* was to use only claims data. Second, the results displayed in our analyses represent more conservative estimates (smaller reductions in emergency care utilization after a treatment change). Finally, we would have had to exclude nearly two-thirds of the patients in our study, resulting in a substantial loss of power and an increased chance for selection bias.

T1DM patients identified in this study may not be representative of the general pediatric T1DM population in the United States. As the dependents of active and past military personnel, patients in this study are likely demographically different than the general US pediatric population and likely experience different levels of healthcare. However, we have no reason to believe that the treatment effects described in our study would vary greatly among different populations.

Conclusion

The purpose of this study was to estimate the effects of continuous subcutaneous insulin infusion and continuous glucose monitoring on utilization of emergency care in an observational cohort of pediatric patients with type 1 diabetes. Patients in our study experienced, on average, approximately two emergency care days annually. We found that patients initiating CSII and/or CGM experienced a statistically significant reduction in the number of days utilizing emergency care.

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Tables

Table 1: Patient Characteristics (n=3,138).

Patient Characteristic	All Patients (N=3,138)
Gender [n (%)]	
Female	1369 (43.6%)
Male	1769 (56.4%)
Age [mean (SD)]	13.8 (3.6)
Patients with Index BMI Value [n (%)]	1515 (48.3%)
Body Mass Index [mean (SD)]	23.6 (5.2)
Patients with Index HbA1c Value [n (%)]	1076 (34.3%)
Hemoglobin A1c [mean (SD)]	9.3 (2.3)
Military branch [n (%)]	
Army	1249 (39.8%)
Coast Guard	69 (2.2%)
Air Force	815 (26.0%)
Marine Corps	221 (7.0%)
Navy	768 (24.5%)
Other	16 (0.5%)
Geographic region [n (%)]	
West	373 (11.9%)
Central	438 (14.0%)
Northeast	1154 (36.8%)
Southeast	968 (30.8%)
Alaska/Hawaii	113 (3.6%)
Non-US	92 (2.9%)
Rank of Sponsor [n (%)]	
Enlisted, Junior	236 (7.5%)
Enlisted, Senior	2297 (73.2%)
Warrant Officer	82 (2.6%)
Officer, Junior	134 (4.3%)
Officer, Senior	388 (12.4%)
Other	1 (0.0%)

Table 2: Treatment Patterns (n=3,138).

Patient Characteristic	All Patients (N=3,138)
Patients with No Treatment Change	1,964 (62.6%)
Patients with Treatment Change	1,174 (37.4%)
Patients with Switch to CSII Only	681 (58.0%)
Patients with Augment with CGM Only	118 (10.1%)
Patients with Switch and Augment	375 (31.9%)

Table 3: Effect of CSII and CGM on Total Emergency Care Days (n=3,138).

Effect	Model					
	Bivariate		Full		Final*	
	RR (95% C.L.)	p-value	RR (95% C.L.)	p-value	RR (95% C.L.)	p-value
CSII	0.77 (0.74, 0.80)	<0.0001	0.81 (0.78, 0.84)	<0.0001	0.81 (0.78, 0.84)	<0.0001
CGM	0.84 (0.80, 0.89)	<0.0001	0.89 (0.81, 0.97)	0.01	0.88 (0.80, 0.96)	0.006
CSII*CGM Interaction	N/A		1.18 (1.05, 1.32)	0.007	1.19 (1.06, 1.34)	0.003
CSII and CGM	N/A		0.84 (0.79, 0.90)	<0.0001	0.85 (0.79, 0.90)	<0.0001

RR: Rate Ratio

*The final Zero Inflated Poisson regression model was adjusted for gender, age, military rank of sponsor, and geographic region, and the zero-model was adjusted for gender, age, military rank of sponsor, and geographic region. Detailed statistical results are displayed in Appendix Table 2.

Table 4: Effect of CSII and CGM on Hospitalization Days (n=3,138).

Effect	Model					
	Bivariate		Full		Final*	
	RR (95% C.L.)	p-value	RR (95% C.L.)	p-value	RR (95% C.L.)	p-value
CSII	0.72 (0.69, 0.75)	<0.0001	0.75 (0.71, 0.78)	<0.0001	0.75 (0.71, 0.78)	<0.0001
CGM	0.82 (0.77, 0.87)	<0.0001	0.89 (0.79, 0.99)	0.03	0.89 (0.79, 0.99)	0.03
CSII*CGM Interaction	N/A		1.21 (1.05, 1.39)	0.008	1.21 (1.05, 1.40)	0.008
CSII and CGM	N/A		0.80 (0.74, 0.87)	<0.0001	0.80 (0.74, 0.87)	<0.0001

RR: Rate Ratio

*The final Zero Inflated Poisson regression model was adjusted for gender, age, military branch of sponsor, and geographic region, and the zero-model was adjusted for gender, age, military rank of sponsor, and geographic region. Detailed statistical results are displayed in Appendix Table 3.

Table 5: Effect of CSII and CGM on ER/Ambulance Days (n=3,138).

Effect	Model					
	Bivariate		Full		Final*	
	RR (95% C.L.)	p-value	RR (95% C.L.)	p-value	RR (95% C.L.)	p-value
CSII	0.85 (0.81, 0.89)	<0.0001	0.93 (0.88, 0.99)	0.02	0.94 (0.88, 0.99)	0.02
CGM	0.89 (0.82, 0.96)	0.002	0.84 (0.73, 0.97)	0.02	0.85 (0.75, 0.97)	0.02
CSII*CGM Interaction	N/A		1.34 (1.12, 1.59)	0.001	1.31 (1.11, 1.54)	0.001
CSII and CGM	N/A		1.04 (.96, 1.14)	0.28	1.04 (0.96, 1.13)	0.32

RR: Rate Ratio

*The final Zero Inflated Poisson regression model was adjusted for gender, age, military branch of sponsor, military rank of sponsor, and geographic region, and the zero-model was adjusted for gender, military branch of sponsor, and military rank of sponsor. Detailed statistical results are displayed in Appendix Table 4.

Table 6: Comparison of Treatment Effects (n=3,138).

Comparison	RR	p-value
CSII and SMBG vs. MDI and SMBG	0.81	<0.0001
MDI and CGM vs. MDI and SMBG	0.88	0.006
CSII and CGM vs. MDI and SMBG	0.85	<0.0001
CSII and SMBG vs. MDI and CGM	0.92	0.10
CSII and CGM vs. MDI and CGM	0.96	0.51
CSII and CGM vs. CSII and SMBG	1.05	0.21

Table 6 displays a comparison of treatment effects from all treatment combinations of multiple daily injections (MDI), self-monitoring of blood glucose (SMBG), continuous subcutaneous insulin infusion (CSII), and continuous glucose monitoring (CGM). RR: Rate Ratio.

Table 7: Effect of CSII and CGM on Diabetes Related Total Emergency Care Days (n=3,138).

Effect	Model					
	Bivariate		Full		Final*	
	RR (95% C.L.)	p-value	RR (95% C.L.)	p-value	RR (95% C.L.)	p-value
CSII	0.83 (0.79, 0.86)	<0.0001	0.90 (0.85, 0.94)	<0.0001	0.90 (0.86, 0.94)	<0.0001
CGM	0.81 (0.76, 0.86)	<0.0001	0.90 (0.80, 1.01)	0.07	0.90 (0.84, 0.97)	0.003
CSII*CGM Interaction	N/A		N/A	0.65	N/A	0.43

RR: Rate Ratio

*The final Zero Inflated Poisson regression model was adjusted for gender, age, military rank of sponsor, and geographic region, and the zero-model was adjusted for gender, age, military rank of sponsor, and geographic region. Detailed statistical results are displayed in Appendix Table 5.

Table 8: Effect of CSII and CGM on Diabetes Related Hospitalization Days (n=3,138).

Effect	Model					
	Bivariate		Full		Final*	
	RR (95% C.L.)	p-value	RR (95% C.L.)	p-value	RR (95% C.L.)	p-value
CSII	0.80 (0.76, 0.83)	<0.0001	0.87 (0.83, 0.92)	<0.0001	0.87 (0.83, 0.92)	<0.0001
CGM	0.77 (0.72, 0.83)	<0.0001	0.80 (0.70, 0.92)	0.001	0.81 (0.71, 0.92)	0.002
CSII*CGM Interaction	N/A		1.19 (1.01, 1.41)	0.04	1.18 (1.01, 1.40)	0.049
CSII and CGM	N/A		0.83 (0.76, 0.92)	0.0002	0.84 (0.76, 0.92)	0.0001

RR: Rate Ratio

*The final Zero Inflated Poisson regression model was adjusted for gender, age, military branch of sponsor, and geographic region, and the zero-model was adjusted for gender, age, military rank of sponsor, and geographic region. Detailed statistical results are displayed in Appendix Table 6.

Table 9: Effect of CSII and CGM on Diabetes Related ER/Ambulance Days (n=3,138).

Effect	Model					
	Bivariate		Full		Final*	
	RR (95% C.L.)	p-value	RR (95% C.L.)	p-value	RR (95% C.L.)	p-value
CSII	0.87 (0.81, 0.92)	<0.0001	1.01 (0.95, 1.08)	0.72	1.01 (0.94, 1.07)	0.86
CGM	0.74 (0.67, 0.82)	<0.0001	0.85 (0.77, 0.95)	0.003	0.88 (0.80, 0.97)	0.008
CSII*CGM Interaction	N/A		N/A	0.99	N/A	0.84

RR: Rate Ratio

*The final Zero Inflated Poisson regression model was adjusted for gender, age, military rank of sponsor, and geographic region, and the zero-model was adjusted for gender, military branch of sponsor, and military rank of sponsor. Detailed statistical results are displayed in Appendix Table 7.

Table 10: Comparison of Main Analysis and Midpoint Sensitivity Analysis (n=3,138).

Treatment	Main Analysis		Midpoint Analysis	
	RR (95% C.L.)	**p-value**	**RR (95% C.L.)**	**p-value**
CSII	0.81 (0.78, 0.84)	<0.0001	0.76 (0.73, 0.79)	<0.0001
CGM	0.88 (0.80, 0.96)	0.006	0.91 (0.83, 1.005)	0.06
CSII*CGM Interaction	1.19 (1.06, 1.34)	0.003	1.14 (1.01, 1.30)	0.03
CSII and CGM	0.85 (0.79, 0.90)	<0.0001	0.79 (0.74, 0.85)	<0.0001

RR: Rate Ratio

Figures

Figure 1: Diagram of patient selection and treatment patterns.

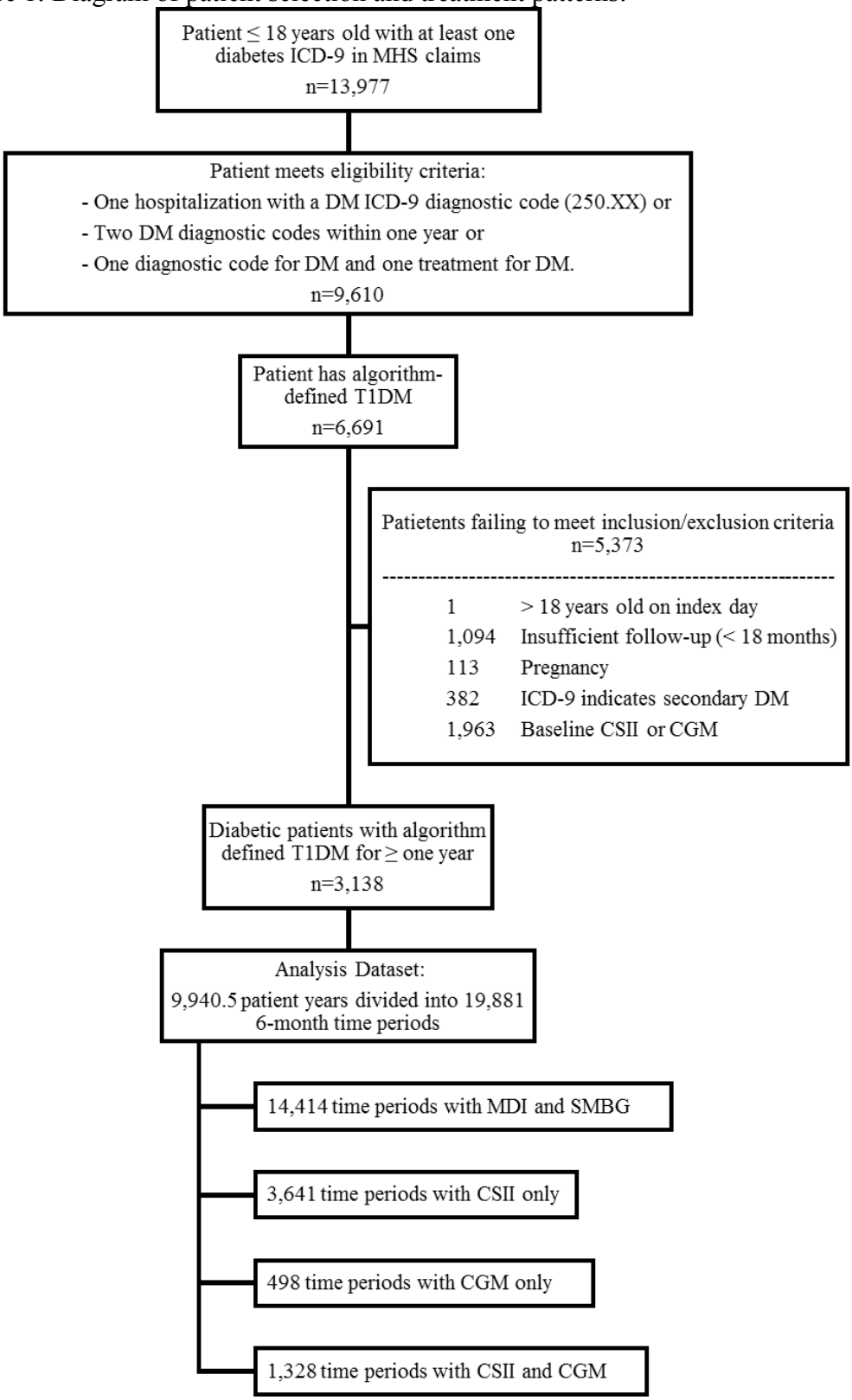

Figure 2: Histogram of total emergency care (n=3,138).

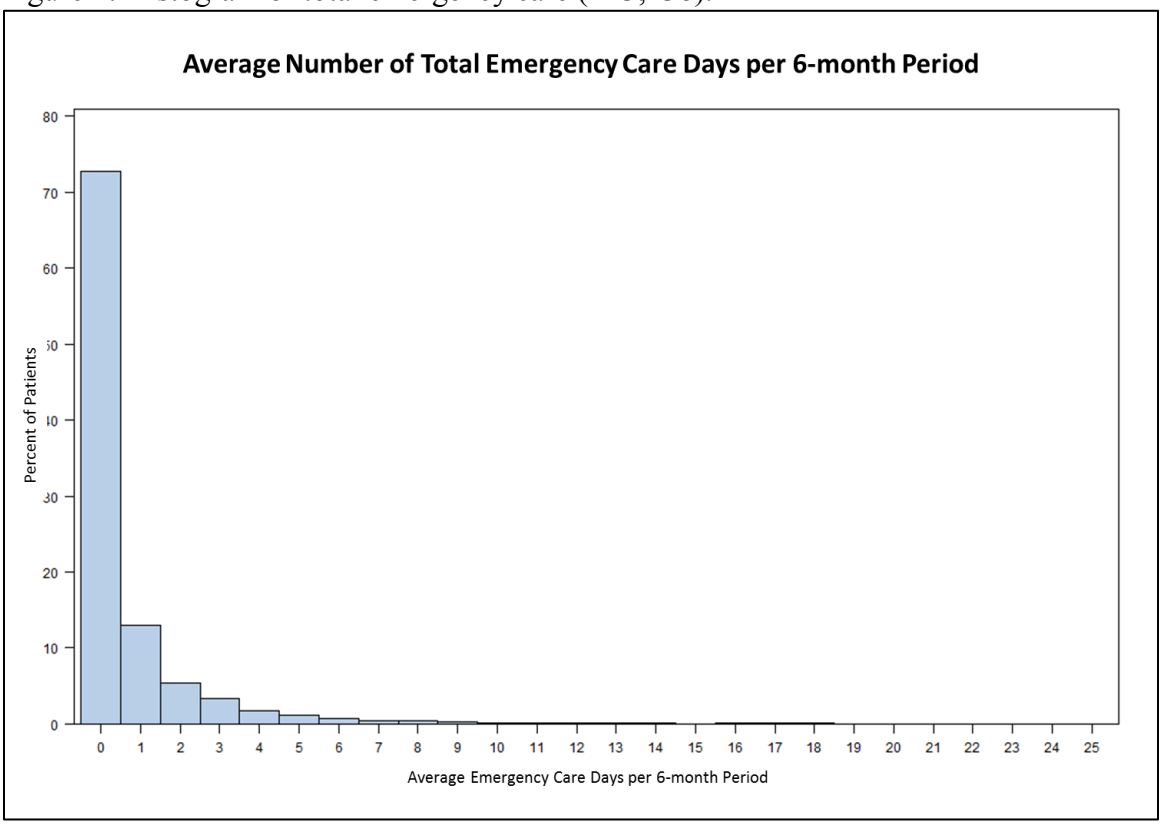

Figure 2 displays the zero-inflated distribution of the average number of total emergency care days per 6-month period.

Figure 3: Histogram of hospitalizations (n=3,138).

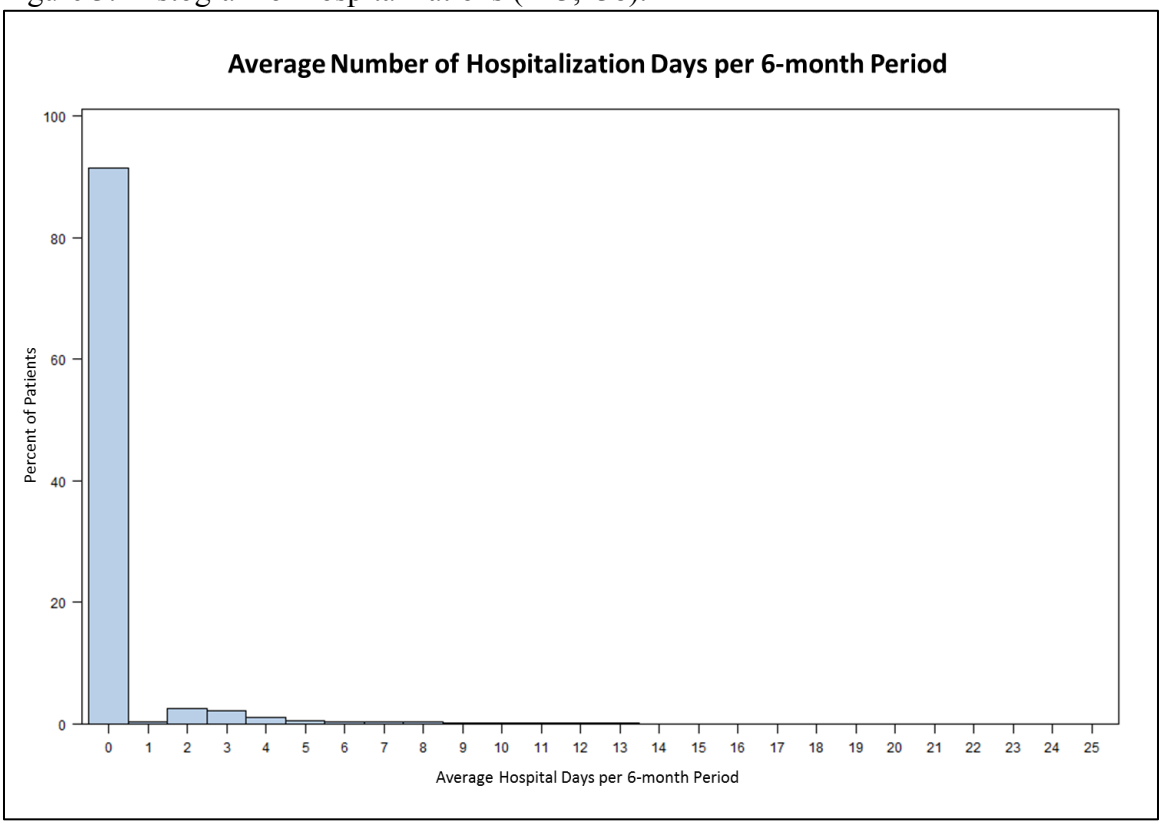

Figure 3 displays the zero-inflated distribution of the average number of hospitalization days per 6-month period.

Figure 4: Histogram of ER/ambulance care (n=3,138).

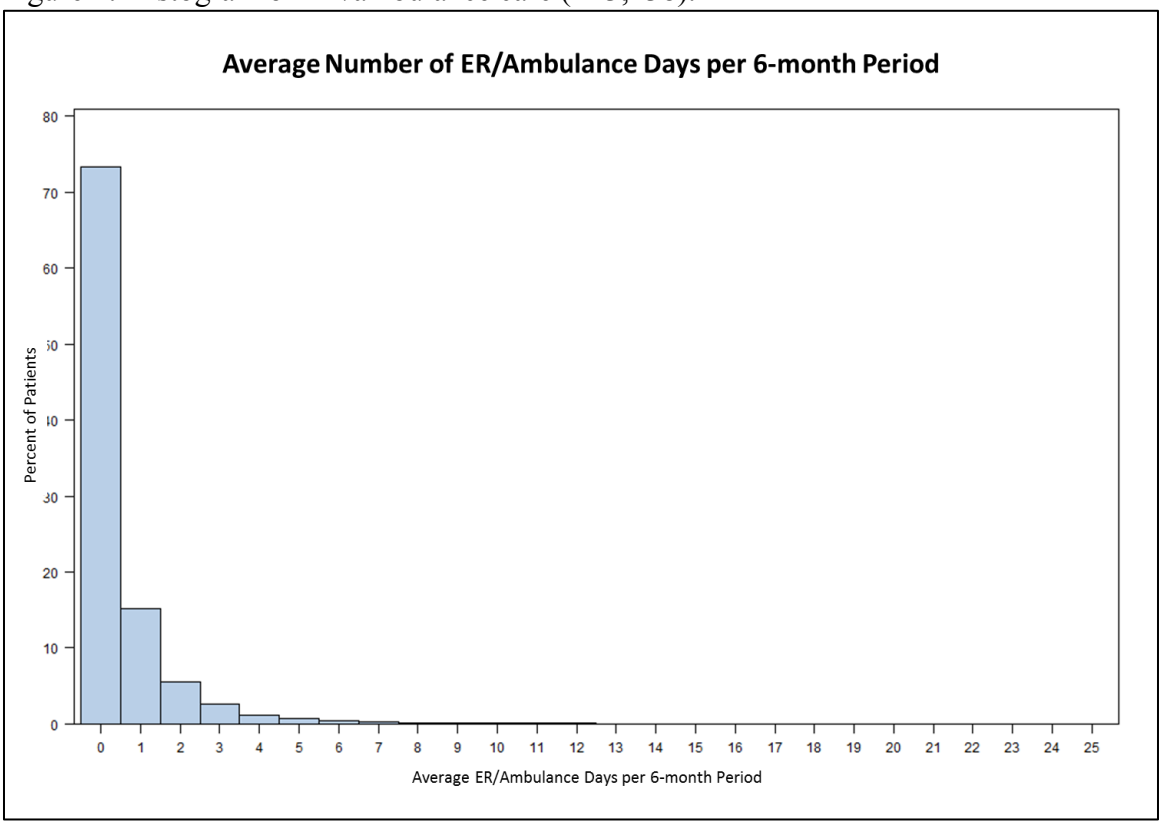

Figure 4 displays the zero-inflated distribution of the average number of ER/ambulance care days per 6-month period.

Appendix Tables

Table A1: Patient Attrition.

Inclusion/Exclusion Criteria	Patients Remaining	Patients Excluded
Patient has a DM Dx	13,977 (100.0%)	
Patient has sufficient DM Dx/med criteria	9,610 (68.8%)	4,367 (31.2%)
Patient has algorithm defined T1DM	6,691 (47.9%)	2,919 (20.9%)
Patient was less than 18 years old at the time of first diagnosis	6,690 (47.9%)	1 (0.0%)
Patient has sufficient follow-up (18 months) enrollment	5,596 (40.0%)	1,094 (7.8%)
Patient not excluded for pregnancy	5,483 (39.2%)	113 (0.8%)
Patient not excluded for condition Dx	5,101 (36.5%)	382 (2.7%)
Patient is at risk of switch and augment	3,138 (22.5%)	1,963 (14.0%)

Appendix Table 1 displays the number of patients excluded and the number of patient remaining after each inclusion/exclusion criteria. These data are also displayed in Figure 1.

Table A2: Effect of CSII and CGM on Total Emergency Care Days – Final Model (n=3,138).

Parameter	Level	RR (95% C.L.)	p-value
CSII		0.81 (0.78, 0.84)	<.0001
CGM		0.88 (0.80, 0.96)	0.006
CSII*CGM Interaction		1.19 (1.06, 1.34)	0.003
Gender	Male vs. Female	0.89 (0.86, 0.91)	<.0001
Age	1 year	1.05 (1.04, 1.05)	<.0001
Rank of Sponsor	Officer v. Enlisted	0.89 (0.85, 0.93)	<.0001
Region	Alaska/Hawaii	0.78 (0.72, 0.85)	<.0001
Region	Central	0.71 (0.67, 0.75)	<.0001
Region	Non-US	0.93 (0.85, 1.03)	0.15
Region	Northeast	0.84 (0.80, 0.87)	<.0001
Region	Southeast	0.68 (0.65, 0.71)	<.0001
Region	West	Ref.	

Appendix Table 2 displays statistical results from our final Zero-Inflated Poisson Regression on the effects of continuous subcutaneous insulin infusion (CSII) and/or continuous glucose monitoring (CGM) on total emergency care days. A summary of these data are also displayed in Tables 3 and 10.
RR: Rate Ratio

Table A3: Effect of CSII and CGM on Hospitalization Days – Final Model (n=3,138).

Parameter	Level	RR (95% C.L.)	p-value
CSII		0.75 (0.71, 0.78	<.0001
CGM		0.89 (0.79, 0.99	0.03
CSII*CGM Interaction		1.21 (1.05, 1.40	0.008
Gender	Male vs. Female	0.93 (0.90, 0.96	<.0001
Age	1 year	1.03 (1.03, 1.04	<.0001
Military Branch	Air Force	1.83 (1.22, 2.75	0.004
Military Branch	Army	1.79 (1.19, 2.69	0.005
Military Branch	Coast Guard	1.59 (1.04, 2.43	0.03
Military Branch	Marine Corps	2.06 (1.37, 3.12	0.0006
Military Branch	Navy	2.04 (1.35, 3.07	0.0007
Military Branch	Other	Ref.	
Region	Alaska/Hawaii	0.86 (0.78, 0.95	0.003
Region	Central	0.84 (0.79, 0.90	<.0001
Region	Non-US	0.91 (0.81, 1.01	0.08
Region	Northeast	0.91 (0.87, 0.96	0.0003
Region	Southeast	0.69 (0.66, 0.73	<.0001
Region	West	Ref.	

Appendix Table 3 displays statistical results from our final Zero-Inflated Poisson Regression on the effects of continuous subcutaneous insulin infusion (CSII) and/or continuous glucose monitoring (CGM) on hospitalization days. A summary of these data are also displayed in Table 4.
RR: Rate Ratio

Table A4: Effect of CSII and CGM on ER/Ambulance Days – Final Model (n=3,138).

Parameter	Level	RR (95% C.L.)	p-value
CSII		0.94 (0.88, 0.99)	0.02
CGM		0.85 (0.75, 0.97)	0.02
CSII*CGM Interaction		1.31 (1.11, 1.54)	0.001
Gender	Male vs. Female	0.91 (0.87, 0.94)	<.0001
Age	1 year	1.08 (1.07, 1.08)	<.0001
Military Branch	Air Force	0.82 (0.53, 1.25)	0.35
Military Branch	Army	0.78 (0.51, 1.19)	0.24
Military Branch	Coast Guard	0.50 (0.32, 0.80)	0.004
Military Branch	Marine Corps	0.68 (0.44, 1.05)	0.09
Military Branch	Navy	0.85 (0.55, 1.30)	0.45
Military Branch	Other	Ref.	
Rank of Sponsor	Officer v. Enlisted	0.67 (0.63, 0.72)	<.0001
Region	Alaska/Hawaii	0.69 (0.61, 0.79)	<.0001
Region	Central	0.66 (0.60, 0.72)	<.0001
Region	Non-US	0.50 (0.41, 0.60)	<.0001
Region	Northeast	0.89 (0.84, 0.95)	0.0002
Region	Southeast	0.93 (0.87, 0.99)	0.03
Region	West	Ref.	

Appendix Table 4 displays statistical results from our final Zero-Inflated Poisson Regression on the effects of continuous subcutaneous insulin infusion (CSII) and/or continuous glucose monitoring (CGM) on ER/ambulance care days. A summary of these data are also displayed in Table 5.
RR: Rate Ratio

Table A5: Effect of CSII and CGM on Diabetes-Related Emergency Care Days – Final Model (n=3,138).

Parameter	Level	RR (95% C.L.)	p-value
CSII		0.90 (0.86, 0.94)	<.0001
CGM		0.90 (0.84, 0.97)	0.003
Gender	Male vs. Female	0.92 (0.89, 0.95)	<.0001
Age	1 year	1.04 (1.04, 1.05)	<.0001
Rank of Sponsor	Officer v. Enlisted	0.82 (0.78, 0.87)	<.0001
Region	Alaska/Hawaii	0.92 (0.83, 1.03)	0.14
Region	Central	0.88 (0.82, 0.94)	<.0001
Region	Non-US	1.35 (1.22, 1.51)	<.0001
Region	Northeast	0.92 (0.87, 0.97)	0.001
Region	Southeast	0.75 (0.71, 0.79)	<.0001
Region	West	Ref.	

Appendix Table 5 displays statistical results from our final Zero-Inflated Poisson Regression on the effects of continuous subcutaneous insulin infusion (CSII) and/or continuous glucose monitoring (CGM) on diabetes-related total emergency care days. A summary of these data are also displayed in Table 7.
RR: Rate Ratio

Table A6: Effect of CSII and CGM on Diabetes-Related Hospitalization Days – Final Model (n=3,138).

Parameter	Level	RR (95% C.L.)	p-value
CSII		0.87 (0.83, 0.92)	<.0001
CGM		0.81 (0.71, 0.92)	0.002
CSII*CGM Interaction		1.18 (1.00, 1.40)	0.049
Gender	Male vs. Female	0.97 (0.93, 1.01)	0.10
Age	1 year	1.04 (1.03, 1.04)	<.0001
Military Branch	Air Force	1.68 (1.12, 2.53)	0.01
Military Branch	Army	1.68 (1.12, 2.54)	0.01
Military Branch	Coast Guard	1.13 (0.72, 1.75)	0.60
Military Branch	Marine Corps	1.66 (1.09, 2.51)	0.018
Military Branch	Navy	2.11 (1.40, 3.19)	0.0004
Military Branch	Other	Ref.	
Region	Alaska/Hawaii	1.10 (0.98, 1.23)	0.10
Region	Central	1.18 (1.10, 1.28)	<.0001
Region	Non-US	1.28 (1.14, 1.44)	<.0001
Region	Northeast	1.08 (1.02, 1.14)	0.01
Region	Southeast	0.86 (0.80, 0.91)	<.0001
Region	West	Ref.	

Appendix Table 6 displays statistical results from our final Zero-Inflated Poisson Regression on the effects of continuous subcutaneous insulin infusion (CSII) and/or continuous glucose monitoring (CGM) on diabetes-related hospitalization days. A summary of these data are also displayed in Table 8.
RR: Rate Ratio

Table A7: Effect of CSII and CGM on Diabetes-Related ER/Ambulance Days – Final Model (n=3,138).

Parameter	Level	RR (95% C.L.)	p-value
CSII		1.01 (0.94, 1.07)	0.86
CGM		0.88 (0.80, 0.97)	0.008
Gender	Male vs. Female	0.88 (0.84, 0.93)	<.0001
Age	1 year	1.08 (1.07, 1.09)	<.0001
Rank of Sponsor	Officer v. Enlisted	0.66 (0.60, 0.72)	<.0001
Region	Alaska/Hawaii	0.63 (0.53, 0.75)	<.0001
Region	Central	0.70 (0.63, 0.77)	<.0001
Region	Non-US	0.51 (0.40, 0.65)	<.0001
Region	Northeast	0.90 (0.84, 0.98)	0.01
Region	Southeast	1.01 (0.93, 1.09)	0.85
Region	West	Ref	

Appendix Table 7 displays statistical results from our final Zero-Inflated Poisson Regression on the effects of continuous subcutaneous insulin infusion (CSII) and/or continuous glucose monitoring (CGM) on diabetes-related ER/ambulance care days. A summary of these data are also displayed in Table 9.
RR: Rate Ratio

CHAPTER 5: SUMMARY AND CONCLUSIONS

Summary

Patient Characteristics

At the time of type 1 diabetes mellitus (T1DM) presentation, 59.2% of patients were admitted to the emergency room and 65.3% were hospitalized. The average BMI at first diagnosis was 20.1 kg/m^2. Females were more likely to use continuous subcutaneous insulin infusion (CSII) and continuous glucose monitoring (CGM); however, once a patient switched to CSII, males and females were equally likely to subsequently add CGM. Females also experienced more ER/ambulance and hospitalization days compared to males. Increased military rank of sponsor, our socio-economic surrogate, was associated with increased CSII and CGM use as well as fewer ER/ambulance, hospitalization days, and total emergency care.

Treatment Patterns

We found the vast majority of incident T1DM patients in our cohort (Aim 1) were using conventional therapy (96.3%) three months after diabetes presentation. More than half (57.14%) of these patients switched insulin delivery from MDI to CSII and about a third (32.62%) augmented with a CGM during follow-up. Greater than 80% of patients who used a CGM initiated CSII concurrently or before CGM use. We found female gender, higher military rank of sponsor, and living in the Central US were the strongest predictors of a treatment switch or augment. We did not detect any changes in CSII use over calendar time (p=0.78); however, there was a very strong relationship between

calendar year of diagnosis and CGM use ($p<0.0001$) showing an increased prevalence in CGM use with each subsequent year.

Hemoglobin A1c

The average hemoglobin A1c measurement for patients in Aim 1 was 8.81%. However, we found values varied wildly during the first 12 to 14 months after first diagnosis. We created a Lowess plot of hemoglobin A1c over time that clearly showed the effects of uncontrolled hyperglycemia at presentation followed by a "honeymoon period" of increased glycemic control. The plot predicted a decrease in hemoglobin A1c from 12.2% at index to 7.2% three months later. Average hemoglobin A1c values then steadily increased until stabilizing at around 8.7% approximately one year after presentation. The average hemoglobin A1c after the first year of diabetes was 8.71%.

In Aim 2, we estimated that patients who switched insulin delivery from MDI to CSII and/or augmented SMBG with CGM experienced statistically significant reductions in hemoglobin A1c at the next measurement. We hypothesized *a priori* that patients who used both CSII and CGM may experience a benefit from both treatments different than the additive benefit of each, but tests for interaction between the two treatments were not statistically significant. However, we did find an interaction between initial hemoglobin A1c and change in treatment so that every 1% increase in A1c above 6% was associated with a 0.19% greater reduction in A1c from a switch and a 0.07% greater reduction from an augment. Thus we predicted clinically meaningful reductions in hemoglobin A1c after a switch or augment were achieved for patients with initial A1c values of 9% and 12%, respectively.

Emergency Care Utilization

In our final analysis (Aim 3), patients utilized 1.29 ER/ambulance days, 1.41 hospital days, and 2.15 total emergency care days per year of follow-up. We estimated that patients who switched from MDI to CSII experienced a decrease in ER/ambulance days (RR = 0.94; $p<0.0225$), hospitalization days (RR = 0.75; $p<0.0001$), and total emergency care days (RR = 0.81; $p<0.0001$). Patients who initiated CGM also had fewer ER/ambulance days (RR = 0.85; $p<0.0196$), hospitalization days (RR = 0.89; $p<0.0306$), and total emergency care days (RR = 0.88; $p<0.0059$). The interaction between CSII and CGM usage was statistically significant in each model, suggesting that patients using CSII and CGM experienced no additional benefit over using CSII (with SMBG) or CGM (with MDI). Our secondary analysis showed CSII and CGM use may play an important role in reducing utilization of emergency care in circumstances where diabetes is secondary to another ailment as well as in diabetes-related situations.

Conclusions

A Brief History of Diabetes

Before the discovery of insulin and its subsequent commercialization as a drug, a diagnosis of type 1 diabetes was equivalent to a death sentence. The characteristics of diabetes were described in Egyptian manuscripts as early as 1500 B.C.[1] Ancient Indian physicians observed ants were attracted to the urine of diabetic patients, thus naming the condition, Madhumeha, meaning "sweet urine disease."[2] The first recorded description using the term 'diabetes,' which literally translates from Greek to mean "siphon," was written in the second century A.D. by Aretaus of Cappodocia who described the disease

as a "melting down of the flesh and limbs into urine."[3] The term 'mellitus,' which means "sweet like honey," was coined in 17th century by British physician Tomas Willis to distinguish diabetes mellitus from diabetes insipidus, where the urine is not sweet.[4,5] Though the sweetness of diabetic urine had been observed for millennia, it was 1775 before glucose was discovered in the urine of diabetic patients.[6] In 1889, Joseph Freiherr von Mering and his colleagues were able to show for the first time that diabetes was a disease of the pancreas by demonstrating that removing the pancreas from dogs subsequently resulted in diabetes.[7]

In the early 1900's the only treatment for diabetes was a starvation diet,[8] and the life expectancy of a juvenile patient diagnosed with diabetes was only 1.3 years.[9] In 1921, Banting and Best were the first to successfully isolate "pancreatic extracts" which were shown to reverse ketoacidosis in dogs.[10] The following year, they published a paper describing the successful treatment of seven human patients with type 1 diabetes[11] marking a turning point where T1DM was a treatable disease for the first time. By 1923, Eli Lilly & Co was producing the first commercially available insulin product, called 'Iletin.' The same year, the Nobel Prize in Physiology or Medicine was awarded to Banting (and Macleod), who shared the prize with Best.

Despite the improvements in insulin extraction and the standardization of therapy in the following decades, outcomes for type 1 diabetic patients continued to be poor. A study published in 1975 estimated the life expectancy of a person diagnosed with type 1 diabetic was reduced by 27 years;[12] though, more recent data has shown life expectancy during this time period was rapidly improving. A 2012 study showed type 1 diabetic

patients diagnosed between 1965 and 1980 had 15 years longer life expectancy compared to patients diagnosed between 1950 and 1964.[13]

The 1970's brought several noteworthy improvements in diabetes care including the first commercially available glucose meter (the Ames Reflectance Meter),[14] the first insulin pumps,[15,16] and characterization of hemoglobin A1c as a biomarker for glycemic control.[17,18] Until the early 1980's, insulin was derived from pork and beef pancreatic extracts. In 1983, human insulin produced by E. coli became the first commercially available recombinant DNA product. Human recombinant DNA insulin had several advantages over animal extracted insulin including improved pharmacokinetics and pharmacodynamics and a more reliable and sustainable supply.[19]

The Diabetes Control and Complications Trial (DCCT) began enrolling patients in 1983 among increasing evidence suggesting that improved glycemic control reduced the risk of microvascular complications from diabetes.[20] The 10-year study showed conclusively that intensive insulin therapy delayed onset and slowed progression of retinopathy and nephropathy in a cohort of type 1 diabetic patients, and these benefits outweighed the observed increased risk of severe hypoglycemia.[21] Results from the DCCT provided the first strong evidence that the chronic complications of T1DM were not inevitable, but could be prevented or delayed with tight glycemic control.

Type 1 Diabetes Today

Many of the tools currently used to treat T1DM were developed in the last two decades. The rapid-acting (Aspart, Lispro, and Glulisine) and long-acting (Detemir and Glargine) insulins commonly used today were developed in the late 1990's and early

2000's. Continuous glucose monitors became available to physicians in the early 2000's and available for personal patient use beginning in 2006. Insulin pumps have also continued to improve and have begun to integrate with CGM technology. Life expectancy continues to increase as a result of improved treatment and management of complications.[22] A Scotish study in 2012 estimated current life expectancy for type 1 diabetic patients is reduced by 11 years for men and 13 years for women.[23]

Significance of Findings

Type 1 diabetic patients have more treatment options today than ever before. Many continue to use conventional therapy, while others choose CSII and/or CGM therapy. However, the treatment patterns of pediatric patients are largely unknown and the benefits of CSII and CGM remain unclear. The purpose of this dissertation was to use observational data to first describe treatment patterns among pediatric patients and then to create estimates of the effects of CSII and CGM use on glycemic control and emergency care utilization. The second and third Aims were designed to answer the question: *Do patients who initiate CSII and/or CGM in a typical care setting experience subsequent improvements in glycemic control?*

Systematic reviews and meta-analyses on CSII and CGM, based largely on clinical trial data, have shown only modest improvements in hemoglobin A1c except among patients with the poorest control.[24,25,26,27,28] By using claims and EMR data, we were able to estimate changes in glycemic control after initiation of CSII and/or CGM among real-world patients who chose to use these treatments. Where clinical trials estimate true treatment effects, we were estimating the actualized benefits patients

experienced from these treatments. It is noteworthy that we measured greater reductions in hemoglobin A1c after initiation of CSII and/or CGM than have generally been described in clinical trials. Consistent with clinical trials, we found that patients with poorer control experienced greater reductions in hemoglobin A1c after a treatment change. It may be that we observed more meaningful improvements in hemoglobin A1c because patients in our cohort had, on average, poorer glycemic control compared to patients included in trials. However, it is also likely that factors which motivated patients in our study to initiate a new therapy also affected subsequent changes in hemoglobin A1c.

Studies suggest a decreased risk of diabetic ketoacidosis (DKA) and severe hypoglycemia (SH) among patients using CSII.[29,30,31] Patients using CGM spend less total time in hypoglycemia,[32] but, the evidence of the effectiveness of CGM use at reducing risk of acute complications of T1DM is mixed. Some studies have shown reduced risk of DKA and/or SH,[33,34,35] while others have found no association.[36,37] We were unable to distinguish between DKA and SH events in our study. However, we estimated a significant reduction in the number of days utilizing emergency care among patients who changed from conventional therapy to CSII and/or CGM suggesting a meaningful reduction in acute complications from diabetes.

The American Diabetes Association recommends pediatric patients maintain a hemoglobin A1c of 7.5% or less,[38] but currently, fewer than one in four US children are meeting this goal,[39] largely due to fear of hypoglycemia. [40,41,42] The results of our analyses suggest patients with poor glycemic control using conventional therapy are likely to experience clinically meaningful improvements in hemoglobin A1c as well as fewer

acute complications after a change in treatment. We believe patients using traditional therapy and not achieving the ADA hemoglobin A1c goal of 7.5% should consider a treatment change to CSII and/or CGM.

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Curriculum Vita

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Education

Johns Hopkins University Expected Graduation: May 2015

- Doctor of Philosophy, Epidemiology
- Concentration: Clinical Trials, Pharmacoepidemiology
- GPA: 3.66
- Dissertation Topic: *Type 1 Diabetes Treatment Patterns and Glycemic Control in a Pediatric Cohort*

George Washington University Graduated: August 2010

- Masters of Public Health, Epidemiology
- Concentration: Infectious Disease Epidemiology
- GPA: 4.00

Kansas State University Graduated: May 2005

- Bachelor of Science, Microbiology
- Bachelor of Science, Biology
- GPA: 3.55

Public Health Experience

Evidera – *formerly United BioSource Corporation* (Bethesda, MD)
Research Associate (June 2011 - Present)

- Lead analyst on projects performing data management and statistical analysis on large, multi-level data sets including medical claims data and electronic medical records
- Assist in the creation of statistical analysis plans for new projects
- Determine hospital catchment areas and calculate incidence and prevalence rates using ArcGIS
- Interpret study results and write reports for company clients
- Co-author abstracts, posters, and manuscripts

George Washington University (Washington, D.C.)
Instructional Assistant: Principles of Epidemiology (7 semesters: Spring 2009 – Fall 2011)
Instructional Assistant: Intro to Geographic Information Systems (3 semesters: Spring and Fall 2009; Spring 2010)

- Instruct small group meetings
- Answer questions regarding assignments
- Facilitate tests and quizzes
- Grade assignments

George Washington University (Washington, D.C.)
Data Analyst (February 2010 - August 2010)

- Perform analysis of covariance (ANCOVA) using SAS to quantify the economic value of volunteer contributions to the Neglected Tropical Diseases Mass Drug Administration in Haiti
- Determine means and frequency distributions of dependent and important independent variables under study

GW Cancer Institute Patient Navigation Research Program (Washington, D.C.)
Assistant to the Data Manager (June 2009 - August 2010)

- Perform data cleaning using SAS
- Assist with quarterly data uploads
- Manage data in Microsoft Access
- Perform various data management tasks

MacroGenics, Inc. (Rockville, MD)
Clinical Practicum (Fall 2009)

- Assist in the development of a risk management plan for a monoclonal antibody being investigated for the prevention of Type 1 Diabetes and other autoimmune disorders
- Conduct literature reviews to characterize identified and potential risks associated with company products and write epidemiological reports of findings

iJet Intelligent Risk Systems (Annapolis, MD)
Health Intelligence Internship (Summer 2009)

- Monitor worldwide health news
- Write situation reports for iJet clients
- Write articles for company publications
- Create disease maps using ArcGIS

Publications

Manuscripts

Robinson DW, Reynolds MW, Casper C, Dispenzieri A, Vermeulen J, Payne K, Schramm J, Ristow K, Desrosiers MP, Yeomans K, Roberts S, Teltsch DY, Swain RS, Habermann TM, Rotella P, Van de Velde H. "Clinical epidemiology and treatment patterns of patients with multicentric Castleman's disease: Results from two US treatment centers." Br J Haematol. 2014 Jan 6.

Posters/Abstracts

Don Robinson Jr, Christin Prutz, Corey Casper, Angela Dispenzieri, Jessica Vermeulen, Helgi van de Velde, Dana Teltsch, Marie-Pierre Desrosiers, Philip Rotella, Richard Swain, Matthew Reynolds. **"**Exploring Rare Disease Epidemiology: Results From a Study in a Lymphoproliferative Disorder, Multicentric Castlemans's Disease." 7th European Conference on Rare Diseases & Orphan Products (ECRD), May 8 – 10, 2014.

Teltsch DY, Swain RS, Robinson DW, Desrosiers MP, Rotella P, Payne KA, Reynolds MW. **"**Estimation of the Incidence Rate of Very Rare Diseases - A Case Study of Multicentric Castleman's Disease." 29th International Conference on Pharmacoepidemiology & Therapeutic Risk Management, August 25 – 28, 2013.

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